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> TRANSACTIONS OF THE TWENTY-EIGHTH ANNUAL MEETING OF THE CENTRAL ASSOCIATION OF OBSTETRICIANS AND GYNECOLOGISTS

Editor in Chief HOWARD C. TAYLOR, JR.

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IOHN I. BREWER · ALLAN C. BARNES

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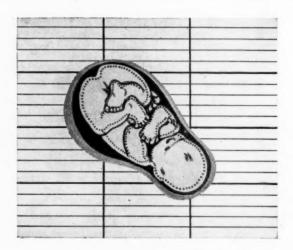
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(1) Stephens, L. J.: Prevention of Premature Delivery: Am. J. Obst. & Gynec. <u>70</u>:6 (June) 1958. (2) Stephens, L. J., in press.



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as of up riduali ed volumes and concentrations. For anesthest eneral use Xylocaine is recommended in conion is mentrat ins of 0.5%, 1% and 2%, with the instance % sol tion generally used for nerve block. % "Xylo linim volumes of 4% Xylocaine may be used redictable opical in those cases where lower concenand woration are ineffective or inadequate. The 4% the low solution may also be used transtracheally and or retabulbar injection.

anesthet indica ons for topical application: Lacerawell tolerions, prasions, burns, corneal analgesia, inis condirect ryngoscopy, pruritus. Indications for inal fluit njecta de anesthesia: suturing, wound closure, spinal" ausalg a, minor surgery, removal of moles, minute warts, and cysts, fracture reduction, bursitis, analgesi post-traumatic syndrome, herpes zoster.

vlocaine®





in



For Infiltration and Nerve Block • Xylocaine HCl 0.5% and 1% without and with epinephrine 1:100,000 in 20 cc. and 50 cc. multiple dose vials, Xylocaine HCl 2% without and with epinephrine 1:100,000 in 20cc. and 50cc. multiple dose vials; also 2 cc. ampules (10's and 30's).

For Spinal Anesthesia ■ Xylocaine HCl 5% with glucose 7.5% (specific gravity 1.030-1.035) in 2 cc. ampules (10's and 100's).

For Peridural Anesthesia • Xylocaine HCl 0.8% and 1.2% without and with epinephrine 1:200,000 in 30 cc. single dose containers. For Continuous Peridural Anesthesia • Xylocaine HCl 1% without epinephrine in 100 cc. single dose containers.

For Transtracheal Use and For Retrobulbar Injection • Xylocaine HCl 4% without epinephrine in 5 cc. ampules (10's).

For Topical Application Mylocaine HCl 0.5% and 1% without and with epinephrine 1:100,000 in 20 cc. and 50 cc. multiple dose vials. Xylocaine HCl 2% without and with epinephrine 1:100,000 in 20 cc. and 50 cc. multiple dose vials; also 2 cc. ampules (10's and 30's). Xylocaine HCl 4% without epinephrine in 50 cc. screw-cap bottles. (NOTE: This dispensing form is never to be used for injection.) Also available for topical use, Xylocaine Ointment 2.5% and 5%, Xylocaine Jelly 2%, and Xylocaine Viscous 2%.

Write for additional complete information concerning specific Xylocaine usage.

\$Bryce-Smith, R.: Local analgesic drugs, Brit. M.J. 1:1039 (April 2) 1960.

n trichomonas vaginitis "... permanent CURES in 84.6%" = "... symptomatic and bacteriologic CURES" in 100%2 = "symptomatic CURE was obtained in 100%, and bacteriologic CURES in 82.5%"3 in moniliasis "symptomatic CURE was effected in about 80%"4 n mixed infections "complete symptomatic and bacteriologic **CURES** in 92%"³ in endocervicitis 75% "were clinically and bacteriologically (as indicated by vaginal smears and cultures) CURED"5

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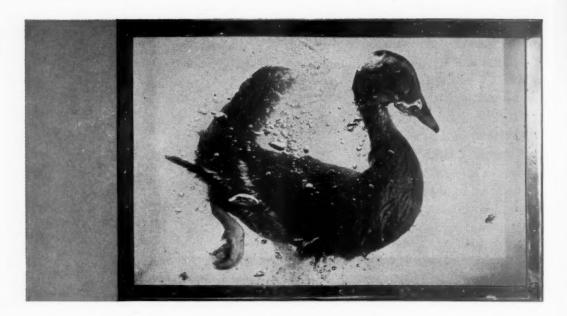
Vaginitis (trichomonal, monilial, nonspecific), Cervicitis

References: 1. Angelucci, H. M.: Am. J. Obst. & Gynec. 50:336, 1945. 2. Hensel, H. A.: Postgrad. Med. 8:293, 1950. 3. Cortese, J. T.: Clin. Med. 2:45, 1955. 4. Dill, L. V., and Martin, S. S.: M. Ann. District of Columbia 17:389, 1948. 5. Horoschak, A., and Horoschak, S.: J. M. Soc. New Jersey 43:92, 1946.

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THE NATIONAL DRUG COMPANY Philadelphia 44, Pa.

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The principle that makes
a duck sink...produces
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SURFACIOLS OF TO PREVENT HARD BRY I SURFACE.

Water doesn't roll off this duck's back... because the water is Surfak-treated. Surfak decreases interfacial tension between water and oil... penetrates the natural oils in the feathers, permits water absorption, adding weight so that the duck sinks.

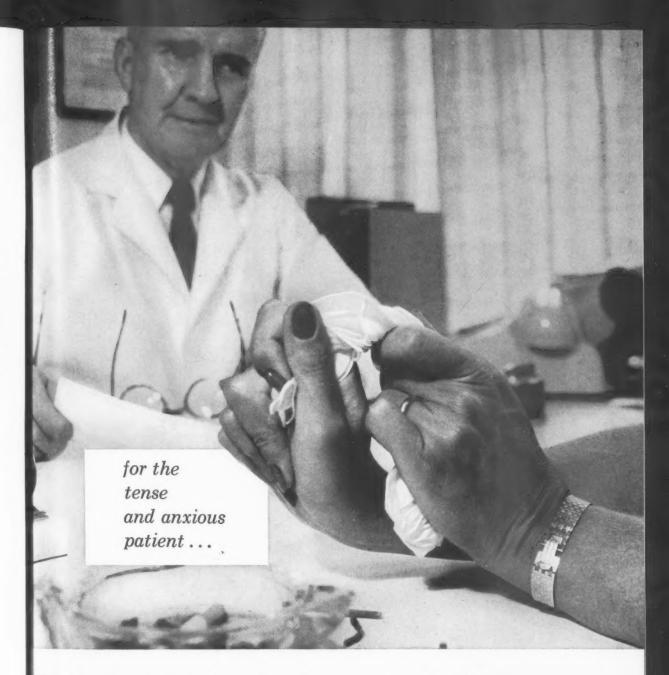
Similarly, in functional constipation, Surfak quickly permeates the heterogeneous fecal mass. The superior surfactant action of calcium bis-(dioctyl sulfosuccinate) reduces the interfacial tension between the aqueous and lipoid phases of the intestinal content to minimal values. The result is soft homogeneous feces which are easily moved to evacuation, naturally.

Adults: One 240 mg. Surfak capsule daily.

Children (and adults with minimal needs): One to three 50 mg. Surfak capsules daily.

240 mg. Surfak capsules in bottles of 15 and 100. 50 mg. Surfak capsules in bottles of 30 and 100.





the only sustained-release tranquilizer that does not cause autonomic side reactions

- SAFE, CONTINUOUS RELIEF of anxiety and tension for 12 hours with purpose just one capsule—without causing autonomic side reactions and without impairing mental acuity, motor control or normal behavior.
- ECONOMICAL for the patient—daily cost is only a dime or so more than for barbiturates.

Meprospan-400

400 mg. meprobamate (Miltown®) sustained-release capsules

Usual dosage: One capsule at breakfast lasts all day; one capsule with evening meal lasts all night.

Available: Meprospan-400, each blue-topped capsule contains 400 mg. Miltown (meprobamate). Meprospan-200, each yellow-topped capsule contains 200 mg. Miltown (meprobamate). Both potencies in bottles of 30.



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When there's apram in her future,

Soon she'll feel the first vague stirrings of new life. And, now, a glass of warm milk does seem to help. It reassures somehow. • But there's much more to it than soothing psychology, isn't there? For it is a time for steppedup calcium intake. Not to mention iron, and the other nutrients she'll draw on. And this is when Pramilets are in order. Filmtab Pramilets give little mother a significant dosage of

phosphorus-free calcium. And, to its already comprehensive formula, Pramilets now adds more iron (easily-tolerated ferrous fumarate) . . . more Vitamin G... more Vitamin $B_6.$ New, improved formula and all, the Pramilets Filmtab is as easy to swallow

as ever. The size hasn't changed. Only the potency.

Comprehensive vitamin-mineral support with just 1 Filmtab daily

Each Pramilets Filmtab represents:

Vitamin A (4000 units) 1.2 mg. (1 MDR*)
Vitamin D (400 units) 10 mcg. (1 MDR)
Thiamine Mononitrate
Riboflavin 2 mg. (13/4 MDR)
Nicotinamide 10 mg. (1 MDR)
Ascorbic Acid (C) 60 mg. (2 MDR)
Pyridoxine Hydrochloride 3 mg.†
Cobalamin (Vit. B ₁₂) 3 mcg.
Calcium Pantothenate 1 mg.††
Calcium Carbonate, U.S.P 625 mg.
GFILMTAD-FILM-SEALED TABLETS, ABBOTT,

[Calcium 250 mg. (1/6 MDR)]
Ferrous Fumarate 120 mg.
[Iron 40 mg. (2½ MDR)]
Magnesium (as oxide) 0.15 mg.
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lodine (as calcium iodate) 0.1 mg. (1 MDR)
Copper (as chloride) 0.15 mg.
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*MDR-Minimum Daily Requirement for Pregnancy. †Recommended Daily Requirement Not Established. ††Supplemental Need in Human Nutrition Not Established.

ALSO NOW AVAILABLE: PRAMILETS-F (Rx ONLY) WITH FOLIC ACID



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"...the most satisfactory drug for use at delivery in the suppression of lactation."2

In over 3,000 patients studied, 1-3 only 3 cases of refilling were reported.

Withdrawal Bleeding Rare, 1-3 since TACE, stored in body fat, is released gradually, even after therapy is discontinued.

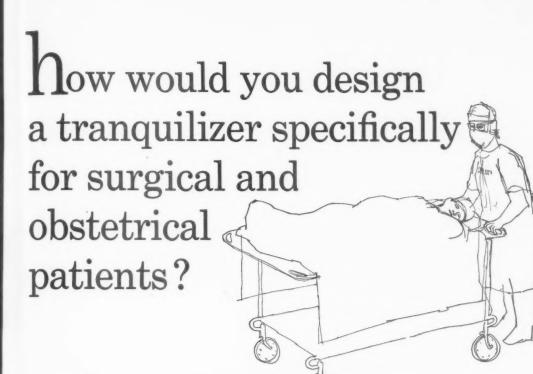
Dosage: 4 capsules daily for 7 days.

Supply: Capsules containing 12 mg. TACE.

References:

M. A. 45:225. 2. Eichner, E., et al.: Obst. & Gynec. 6:511. 3. Nulsen, R. O., et al.: Am. J. Obst. & Gynec. 65:1048.

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wouldn't you

see how closely () these ATARAX want it to: advantages meet your requirements

decrease the need for narcotic pre-medication

"Hydroxyzine hydrochloride [ATARAX] appeared to have . . . a useful influence upon the course of narcosis. The doses of the usual drugs could be reduced by about 30%."1

relieve anxiety connected with labor ATARAX "... is a valuable compound for relief of stress and apprehension... helps the patient to manage her own labor."2

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ATARAX "... produces an ideal preoperative state without depression of vital functions."3

ATARAX is remarkably well tolerated. Why not extend its benefits to all your tense and anxious patients?

Dosage: Atarax parenteral: Pre- and postoperative adjunctive medication: Adults-I.M. or I.V., 25-100 mg.; children-I.M., 0.5 mg./lb. body weight. Pre- and postpartum adjunctive therapy: I.M. or I.V., 25-100 mg. The usual precautions pertaining to parenteral therapy should be observed. Atarax tablets or syrup: Adults-25 mg. t.i.d. to 100 mg. q.i.d. Children-under 6 years, 50 mg. daily; over 6 years, 50-100 mg. daily; in divided doses. Prescription only. References: 1. Ponzi, A.: Minerva anestesiol. 22:306 (Sept.) 1956. 2. Sicuranza, B. J., Tisdall, L. H.: Postgrad. Med. 28:558 (Nov.) 1960. 3. Grady, R. W., and Rich, A. L.: J. M. A. Alabama 29:377 (Apr.) 1960.

(brand of hydroxyzine HCI)



New York 17, N. Y. Division, Chas. Pfizer & Co., Inc. Science for the World's Well-Being®

VITERRA® Capsules-Tastitabs®-Therapeutic Capsules for vitamin-mineral supplementation

for the special laxative needs of pregnancy

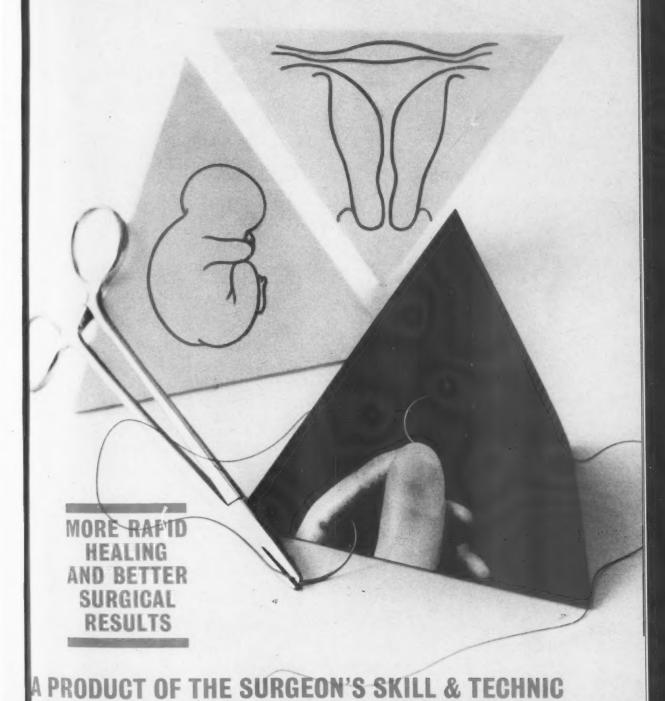
By softening the stool and gently increasing peristalsis, AGORAL safely overcomes the mechanical interference with normal evacuation.

Because AGORAL exerts no action on uterine musculature, it is safe to use during the entire pregnancy. And, patients find its pleasant marshmallow flavor highly acceptable even during long-term usage.



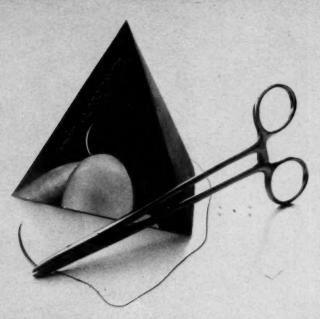
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NEW HIGH TENSILE SURGICAL GUT

increased knot and tensile strength: Exclusive processing methods provide a completely uniform gut of higher knot strength plus improved tensile strength.

softer, smoother strand: Satin matte finish eliminates fraying. Gut is less irritating to tissue and holds knots more securely.

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armed on ATRAUMATIC® NEEDLES: New drilled end design permits uniform tempering of entire needle for greater strength. The needle holder may be placed far back on the needle shaft for greater tissue "bite". Flat surface opposite cutting edge is carried back on the needle shaft for a firm grip in the needle holder.

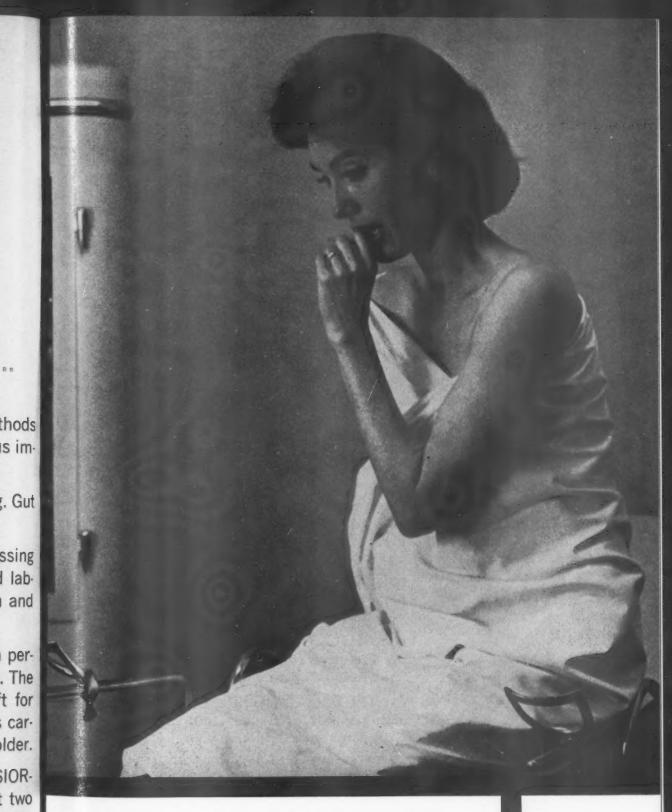
and to assist in episiotomy repair . . . DOUBLE-ARMED EPISIOR-RHAPHY SUTURE. Just cut strand to needed length to get two sutures: one with taper needle for deep tissue work; one with cutting needle for subcuticular stitching and, if desired, skin closure.

All sutures are available in the safer, easy-to-dispense SURGILOPE SP® Sterile Suture Strip Pack—winner of the 1960 Packaging Institute Award for the most outstanding advance in applied packaging technology.

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SURGICAL PRODUCTS DIVISION AMERICAN CYANAMID COMPANY - 30 ROCKEFELLER PLAZA - N. Y., N.Y. - 8ALES OFFICE: DANBURY, COMM.

IN PRU helps y ment w of hydr tiated lieves i ing, and acidity



Stops the itch she dreads to scratch

IN PRURITUS VULVAE—whatever its cause—ES-A-CORT helps you control the intolerable itching and embarrassment within minutes. ES-A-CORT'S balanced combination of hydrocortisone, estrogen, and vitamin A . . . potentiated by DOME'S exclusive ACID MANTLE vehicle . . . relieves inflammation, itching and edema; facilitates healing, and restores the normal tonicity, vitality and protective acidity of mucosa and skin. CAUTION: contraindicated in patients with carcinoma of breast or genitalia.

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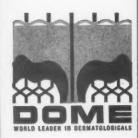
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ES-A-CORT"

CREME (pH 4.6) LOTION micronized hydrocortisone alcohol, vitamin A and estrone in the exclusive ACID MANTLE® Vehicle.

DOME CHEMICALS INC.
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to relieve the symptoms of premenstrual tension

for EDEMA... CYCLEX provides the promp diuresis of HYDRODIURIL for rapid reduction of weight gain, breast fullness, abdominal congestion

for MOOD-CHANGES...CYCLEX supplies the effective relief of meprobamate for nervous ness, irritability, tension, nausea, malaise, insomnia

for GI DISTRESS...CYCLEX affords quick acting relief of nausea and bloating associated with premenstrual tension

SUPPLIED: Tablets, bottles of 100. Each tablet contains 25 mg of HYDRODIURIL (hydrochlorothiazide) and 200 mg. of meprobamate

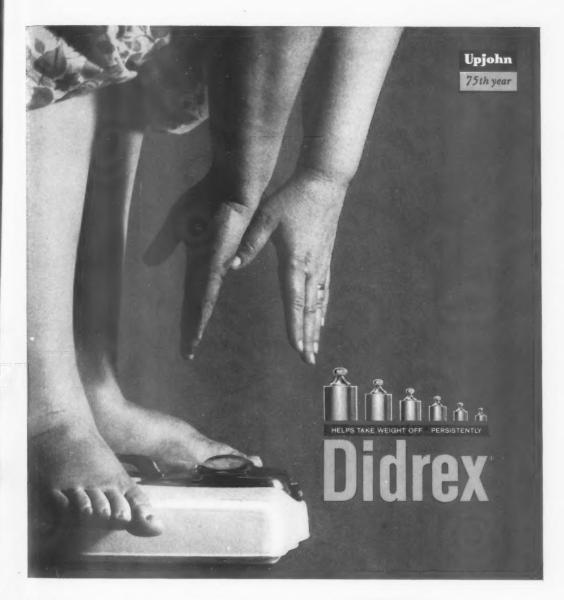
DOSAGE: Usual adult dosage is one tablet once or twice a day, beginning on the first morning of symptoms and continuing until the onset of menses. CYCLEX may be continued through the menstrual period.

Before prescribing or administering CYCLEX, the physician should consult detailed information on use accompanying package or available on request.

CYCLEX and HYDRODIURIL are trademarks of Merck & Co., INC.



MERCK SHARP & DOHME Division of Merck & Co., Inc. West Point, Pa.



Didrex doesn't perform miracles...
it just helps the obese patient do
it herself the recent is simple persistent distributed.

It herself. The reason is simple: persistent, significant loss of weight, up to 30 weeks in reported cases, helps to preclude the "weight plateau" that so often discourages dieters after a few weeks. Thus, time and will become your allies in changing the patient's dietary habits built over months or years of weight accumulation. Didrex may be used in closely supervised diabetic, coronary insufficient, and hypertensive patients.

BRIEF BASIC INFORMATION

Description: Didrex is the Upjohn brand of benzphetamine hydrochloride $\{(+).N\text{-benzyl-N}, \alpha\text{-dimethyl-phenethylamine hydrochloride}\}$. A sympathomimetic compound with marked anorectic action and relatively little stimulating effect on the CNS or cardiovascular system.

Indications: Control of exogenous obesity.

Contraindications: None known to date. However, use with caution in moderate or severe hypertension, thyrotoxicosis, acute coronary disease, or cardiac decompensation.

Dosage: Initiate appetite control with $\frac{1}{2}$ to 1 tablet (25 to 50 mg.) in mid-morning or mid-afternoon, according to the patient's eating habits for several days. Then "adjust" dosage to suit each patient's needs to a maximum of 3 tablets deily (150 mg.).

Side Effects: No effects on blood, urine, renal or hepatic functions have been noted. Minimal side effects have been observed occasionally: dry mouth, insomnia, nausea, palpitations and nervousness.

Supplied: 50 mg., benzphetamine hydrochloride, press-coated, scored tablets, in bottles of 100 and 500.

*Trademark - brand of benzphetamine hydrochloride, Upjohn.

References: 1. Stough, A. R.: Weight loss without diet worry: use of benzphetamine hydrochloride (Didrex). Journal of the Oklahoma State Medical Association, 53:760-767 (November) 1960. 2. Oster, H., and Mediar, R.: A clinical pharmacologic study of benzphetamine (Didrex), a new appetite suppressant. Arizona Medicine, 17:398-404 (July) 1960. 3. Simkin, B., and Wallace, L.: A controlled clinical trial of benzphetamine (Didrex). Current Therapeutic Research, 2:33-38 (February) 1960.

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AGAINST CATHETERS & ENEMAS

Catheters and enemas may be highly useful postoperatively and postpartum, but they are capable of serious drawbacks.

PATIENTS often dislike and fear such instrumentation, sometimes even more than the surgery or delivery that preceded it.

PHYSICIANS are mindful of the frequent risk of infection following catheterization, despite the most painstaking techniques. The passage of a sterile catheter into the bladder may introduce pathogens, since the urethra is not always sterile nor can it be readily sterilized.

NURSES find that catheterization and the administration of enemas require considerable time, which might be advantageously employed for other nursing procedures.



everyone is relieved when URECHOLINE

replaces catheters and enemas

RELIEF FOR THE PATIENT...Prophylactic use of URECHOLINE soon after surgery or childbirth may prevent painful urinary retention and abdominal distention. Therapeutically, URECHOLINE facilitates micturition and defecation by inducing muscular contractions of the bladder and intestinal tract—without subjecting patients to the discomfort of catheters and enemas.

RELIEF FOR THE PHYSICIAN...By obviating instrumentation, URECHOLINE eliminates the danger of infection that may follow it.

RELIEF FOR THE NURSE... Prophylactic and therapeutic use of URECHOLINE makes scarce nursing time available for other purposes.

Dosage: Dosage must be individualized. The usual oral dosage is 10 to 30 mg. three or four times daily. The usual subcutaneous dose is 5 mg. (1 cc.). **Supplied:** Tablets, 5 and 10 mg., bottles of 100. Injection, 5 mg. per cc., amouls of 1 cc.

Additional information on URECHOLINE is available to physicians on request.

MERCK SHARP & DOHME, DIVISION OF MERCK & CO., INC., WEST POINT, PA.

URECHOLINE IS A TRADEMARK OF MERCK & CO. IN

SAFE AND SOUND

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to prevent morning sickness.

With new Tigan 250 mg capsules you can now provide protection against morning sickness with only two capsules daily — one at bedtime and one in the morning. Tigan is so safe that it may be used with confidence as a routine prescription in any pregnancy. Avoiding the risks of phenothiazine derivatives and the limitations of the antihistamines, Tigan acts both therapeutically and prophylactically to stop active vomiting or to prevent nausea and vomiting.

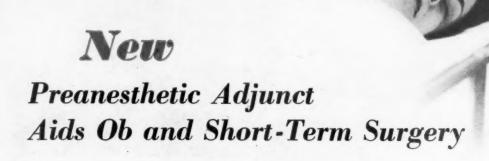
Consult literature and dosage information, available on request, before prescribing.

TIGAN BIBLIOGRAPHY: 1. M. W. Goldberg, paper read at Colloquium on the Pharmacological and Clinical Aspects of Tigan, New York City, May 15, 1959. 2. O. C. Brandman, ibid. 3. J. A. Lucinian and R. H. Bohn, ibid. 4. D. W. Molander, ibid. 5. B. I. Shnider and G. L. Gold, ibid. 6. W. S. Derrick, ibid. 7. B. Wolfson and F. F. Foldes, ibid. 8. L. McLaughlin, ibid. 9. W. K. Gauthier, Discussant, ibid. 10. H. E. Davis, Discussant, ibid. 11. I. Roseff, W. B. Abrams, J. Kaufman, L. Goldman and A. Bernstein, J. Newark Beth Israel Hosp., 9:189, 1958. 12. W. Schallek, G. A. Heise, E. F. Keith and R. E. Bagdon, J. Pharmacol. & Exper. Therap., 126:270, 1959. 13. W. B. Abrams, I. Roseff, J. Kaufman, L. M. Goldman and A. Bernstein, New York J. Med., 59:4217, 1959. 14. O. W. Doyle, Clin. Med., 7:43, 1960. 15. L. A. Nathan, Curr. Therap. Res., 2:6, 1960. 16. Council on Drugs, New and Nonofficial Drugs, J.A.M.A., 172:1038, 1960. 17. O. L. Davidson, J. Tennessee M.A., 53:140, 1960. 18. O. Brandman, Gastroenterology, 38:777, 1960. 19. B. A. Robin, Maryland M. J., in press. 20. A. L. Kolodny, Am. J. M. Sc., 239:682, 1960. 21. F. Cacace, Colorado GP, 2:5, 1960. 22. J. W. Bellville, I. D. J. Bross and W. S. Howland, Clin. Pharmacol. & Therap., in press. TIGAN® Hydrochloride-4-(2-dimethylaminoethoxy)-N-(3,4,5-trimethoxybenzoyl) benzylamine hydrochloride



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for faster, more prolonged, more effective antiemetic activity



LOT GODO Propiomazine Hydrochloride, Wyeth

acts for 3-4 hours cuts recovery-room time

Predictable, short-acting LARGON provides sedation that relieves apprehension and produces a light sleep. It enhances the action of analgesics and anesthetics, reducing the need for CNS depressants and extending the margin of safety. Its short action, similar to meperidine, permits repeat doses without overlapping effect. Also provides antiemesis. LARGON has not been observed to produce maternal or fetal depression, jaundice or blood dyscrasias, or adverse cardiovascular effects.

Supplied: Largon, 20 mg. per cc. in Water for Injection U.S.P., available in ampuls of 1 and 2 cc., packages of 25. For further information on prescribing and administering Largon, consult current Direction Circular enclosed with medication, or available on request.



Wyeth Laboratories Philadelphia 1, Pa.

METRECAL AND OBESITY

A DISCUSSION: PART I

the first of two parts of a discussion on the significance of Metrecal in the management of obesity



THE EDWARD DALTON COMPANY

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Pa.

A Division of Mead Johnson & Company



METRECAL AND OBESITY

From the time of its introduction in late autumn of 1959, the professional acceptance of Metrecal brand dietary for weight control—the product and the concept—has been widespread and sustained.

During this brief interval a considerable body of successful experience has accrued —both from clinical studies and physician observation.

During the same period, many questions have arisen (some fundamental) and have gained some attention, with relation to the safety and efficacy of the product in the personal and professional management of obesity.

The incidence of such questions is not unexpected in view of the fact that Metrecal is an essentially simplified approach to overweight, a problem that (1) is one of the oldest of the chronic ills of man, (2) is widespread in the United States today in the sense of including virtually half of the adult population, and (3) is dangerous both as such and for the degree to which it aggravates other disease entities.

These questions have resulted in an element of confusion which has been compounded by a host of products which (while seemingly imitative to the concept) offer a wide degree of variability in (1) their nutritional composition, (2) the extent of their technical validation, and (3) the responsibility of their accompanying claims.

This, therefore, is the first of a discussion in two parts, prepared expressly for the medical and allied professions.

Part I of this discussion begins with a restatement of certain aspects of obesity which are fundamental to sound diagnosis and therapy, notwithstanding the apparently elementary principles they represent. With these clearly in mind, Metrecal, both concept and product, will thereafter be evaluated in detail.

Part II of this discussion will be published shortly in this journal and will be concerned with clinical evidence and other supportive data which clearly substantiate the medical and nutritional rationale for Metrecal as presented here. In these terms, it should be possible objectively and constructively to comment on such topics, as: (1) its safety and effectiveness for short- and long-term use; (2) practicability in use in comparison with restricted diet or appetite-depressant drugs, and (3) whether it militates against the return to so-called "usual foods" or dietary regimens conducive to the cohesiveness of the family as a social unit.

Metrecal is supported on a continuing basis by clinical investigations of considerable scope and penetration. The practice-oriented data resulting from these studies will be similarly presented from time to time as a service to the medical and allied professions, in future issues of this journal.

OBESITY

Elementary considerations

Obesity is due to the intake of more energy than is expended, *i.e.*, simple overeating as compared to needs.

When seeing an obese patient for the first time, a physician's thoughts may be summarized as follows:

Why is the patient obese?

Is obesity due to psychological or emotional factors? neurosis? loneliness? disappointment? boredom? compulsion? or is it due to an attempt to escape from an unfeeling world?

Is overeating related to the eating habits of the family?

Is there an endocrine imbalance as a basis for obesity?

Is obesity in this patient a familial tendency? Are siblings likewise obese?

Is the patient a between-meal "nibbler"?

How can I most successfully persuade this patient to reduce?

I can advise, and encourage;

I can appeal to a desire for an improved appearance;

I can frighten with facts on the susceptibility of obese older persons to degenerative diseases (such as diabetes, arteriosclerosis and heart disease);

I can emphasize the increased comfort and mobility that comes from reducing—no more abdominal supports, or tight-fitting clothes, or wheezing, or being laughed at;

Since obesity is a symptom, I can try to determine the primary cause and establish a reasonable goal (weight loss, and at least partial resolution of the primary cause) toward which the patient can strive;

I can emphasize the decreased life expectancy of the obese;

I can explain the increased risk, and longer convalescence, if extensive surgery is ever needed.

What are the real dangers (or "costs") of overweight?

1. Increased rate of mortality (shorter life on the average);

- 2. Appearance not as socially acceptable;
- 3. Reduced physical capacity and mobility;
- 4. Increased susceptibility to certain degenerative diseases: diabetes, arteriosclerosis, heart disease;
- 5. Increased surgical risk.

What can I do to aid this patient?

Prescribe drugs to reduce appetite! But I know their effects are short-lived and they may have some undesirable reactions.

Undertake psychotherapy! But this is time-consuming and expensive. I can be most effective by just listening and counseling.

Suggest a low-calorie diet of usual foods! But this usually is not very successful because what is intended as a 1000-calorie diet may end up as a 2000-calorie intake, and the patient gets discouraged because significant weight loss is not achieved. I haven't time to discuss with each patient the thermal qualities of each food and its calorie equivalent—and most patients couldn't care less.

Educate the patient to proper eating habits! This is the essence of the problem. To develop adequate motivation, significant weight loss must be attained promptly, without excessive hunger, with adequate nutrition, with a minimum of temptation, and with the avoidance of decisions on whether to eat or not to eat attractive high-calorie foods, and how much.

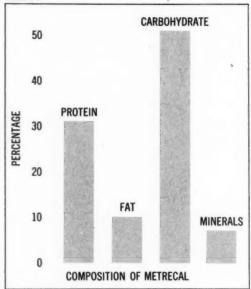
Now, the physician can prescribe a dietary for weight control that was designed to meet the basic medical objectives necessary for intelligent management of the obese patient. This means the complete substitution of a measured amount of a nutritionally adequate food for all usual foods for a period of time.

WHAT IS METRECAL?

The abbreviated charts on the following pages describe the composition, analysis, essential features, and qualities of Metrecal dietary for weight control. These seemingly elementary considerations describe a product designed to meet a widespread therapeutic need; adequately, uniquely, safely, and simply.

METRECAL AND OBESITY

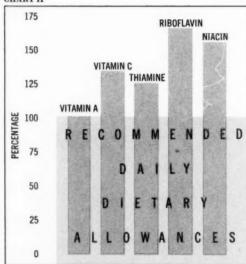




the composition of Metrecal

Metrecal contains a high percentage of protein and a moderate amount of fat. These contribute to the appetite- and hunger-satisfying qualities of Metrecal.

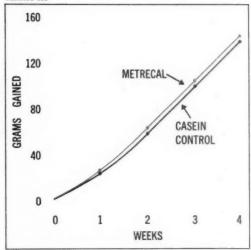
CHART II



vitamins in Metrecal

Metrecal supplies even more vitamins than recommended for the average adult. Vitamins are essential to health, and all are present in adequate amounts in Metrecal.

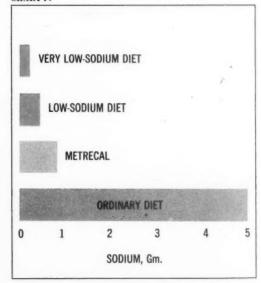
CHART III



Metrecal is nutritionally complete

The rate and amount of gain in body weight are identical for growing rats fed Metrecal or a casein control ration ad libitum. This indicates that Metrecal is a nutritionally complete food.

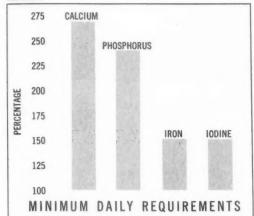
CHART IV



sodium content of Metrecal

Metrecal supplies approximately 900 mg. of sodium per 900 calories. This is a desirable intake for obese or hypertensive patients. Where profuse sweating occurs, the ingestion of additional salt may be specified.

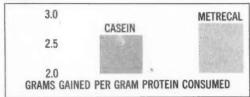
CHART V



minerals in Metrecal

Metrecal provides from 150% to 266% of the Minimum Daily Requirements for calcium, phosphorus, iron and iodine. Metrecal also supplies adequate amounts of all other minerals known to be required by normal persons.

CHART VI



Metrecal protein is nutritious

Evaluation of the nutritional quality of the protein in Metrecal shows that the protein is as nutritious as casein—the standard for such studies.

CHART VII

	QUALITY-C	ONTROL TEST	S ON METRECAL	
	INGREDIENTS		FINISHED PRODUCT	
0	100	200	300	400
	1	NUMBER OF TI	ESTS	

Metrecal is a quality product

Metrecal is **tested thoroughly**—396 tests and assays are completed before Metrecal is released.

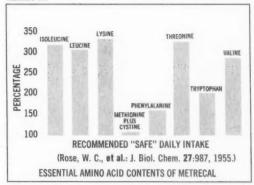
CHART VIII

	FATTY AC	CID CONT	ENTS OF M	ETRECAL	
7-1100	FUNSATURATED ESSENTIAL	UNSATU	IRATED	SATURATE	D
0	20	40	60	80	100
		PERC	ENTAGE		

essential fatty acids in Metrecal

Metrecal supplies ample quantities of the **polyunsaturated** "essential **fatty acids."** Linoleic and linolenic acids constitute 33% of the fatty acid contents of Metrecal, and more than % of the fatty acids in Metrecal are unsaturated.

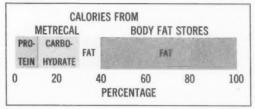
CHART IX



amino acid content of Metrecal is ample

Metrecal supplies significant amounts of all amino acids, including **ample quantities of each amino acid** which is essential in human nutrition.

CHART X



Metrecal is effective

Calories are required to maintain body temperature and support muscular activity. If an obese sedentary person requires 2300 calories and ingests 900 calories as Metrecal, there will be a "calorie deficit" of 1400 calories. This will be met by oxidation of body fat, as shown in the chart. Such a person, limited strictly to 900 calories per day as Metrecal, would lose 2.4 pounds of fat each week.

METRECAL AND OBESITY

The foregoing Part I of a DISCUSSION on the above subject has summarized certain elementary concepts on obesity and defined Metrecal.

In Part II of this DISCUSSION, to be published soon in this journal, the Edward Dalton Company will summarize the clinical data¹⁻⁴ validating the effectiveness of Metrecal, and comment on certain misconceptions arising from its successful attack on the problem of obesity in American life.

References: (1) Antos, R. J.: Southwestern Med. 40:695-697 (Nov.) 1959. (2) Roberts, H. J.: Am. J. Clin. Nutrition 8:817-832 (Nov.-Dec.) 1960. (3) Tullis, I. F.: J. Mississippi M. A. 1:636-638 (Dec.) 1960. (4) Tullis, I. F. and Allen, C. E.: Clinical Experiences with a Simple Weight-Reducing Formula, Current Therapeutic Research, in press.





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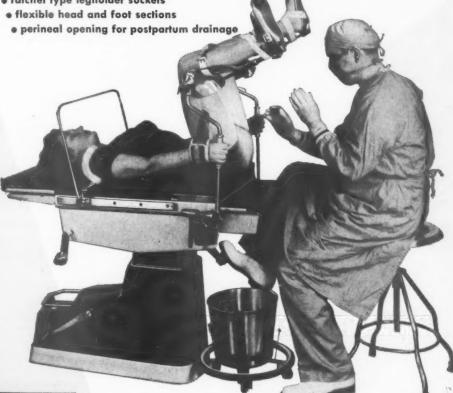
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... so completely fresh in its design approach as to be truly revolutionary in its convenience and control for operative as well as perineal route delivery.

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- . so advanced in its suspension, positioning and optical system as to establish new standards for obstetrical illumination.
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After episiotomy

What now?



Chymar; for one thing

THE SUPERIOR SYSTEMIC ANTI-INFLAMMATORY ENZYME

to control inflammation, swelling, and pain in EPISIOTOMIES, pelvic inflammatory disease, post-partum breast engorgement, thrombophlebitis.

Chymar reduces inflammation and edema of tissues, hastens absorption of blood extravasates, diminishes pain, and thus promotes smoother healing. More than 80% of episiotomies have shown complete relief of edema in the wound, and in no case was it necessary to release sutures.¹ Chymar also reduces pain and engorgement in the postpartum breast.² In pelvic inflammatory disease, Chymar has reduced inflammation, swelling and pain in 85% of patients.³ And in thrombophlebitis, Chymar rapidly diminishes pain, swelling and tenderness around the vein; allows earlier activity of the patient.⁴

1. Fullgrabe, E. A.: Ann. New York Acad. Sc. 68:192, 1957. 2. Clinical Reports to the Medical Department, Armour Pharmaceutical Company, 1960. 3. Reich, W. J., and Nechtow, M. J.: Am. Pract. & Digest Treat. 11:45, 1960. 4. Teitel, L. H.; Siegel S. J.; Tendler, J.; Reiser, P., and Harris, S. B.: Indust. Med. & Surg. 29:150, 1960.

the systemic route to faster healing at any location

ARMOUR PHARMACEUTICAL COMPANY KANKAKEE, ILLINOIS Armour Means Protection

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Chymar Aqueous and Chymar (in oil) contain chymotrypsin, a proteolytic enzyme with systemic anti-inflammatory and antiedematous properties. ACTION: Reduces inflammatiory and all types; reduces and prevents adema except that of cardiac or remalorigin; hastens absorption of blood and lymph extravasates; restores local circulation; promotes healing; reduces pain. INDICATIONS: Chymar is indicated in respiratory conditions to liquefy thickaned secretions and suppress inflammation of mucosa and bronchiolar tissue; in accidental trauma to speed reduction of hematoma and edems; in inflammatory demantoses to ameliorate acute inflammation in conjunction with standard therapies; in gynecologic conditions to suppress inflammation and deema and stimulate healing; in surgical procedures to minimize surgical trauma with inflammation and swelling; in genito-urinary disorders to reduce pain and promote faster resolution; in ophithalmic and olothinol aryngic conditions to lessen hematoma, edema and inflammatory changes; in dental procedures to lessen pain and gum tissue trauma, with inflammation and swelling, in reaction to extraction surgery. PRECAUTIONS: Chymar and chymar Aqueous are for intramuscular injection only. Although sensitivity to chymotrypsin is uncommon, altergic or anaphylactic reactions may occur as with any foreign protein. The usual remedial agents should be readif-available in case of untoward reaction. Precautions (scratch test ing for Chymar, scratch or intradermal testing for Chymar, Aqueous should be exercised in those patients with known or suspected altergies or sensitivities. DOSAGE: 05. Co. to 1.0 c. c. deep inframuscularly once or twice daily, depending on severity of condition or recurrent conditions, 9.5 cc. to 1.0 c. c. conce or twice weekly SUPPLIED: 5 cc. vials, 5000 Armeer Units of proteolytic activity per cc.

Jan. 1961, A.P. Co.



NEWRADIOPAQUE PENROSE DRAINS

DAVOL



TWO major improvements that provide a greater sense of security for patient, hospital and physician:

- 1. CENTIMETER CALIBRATION: Permits rapid, accurate evaluation of the length of the indwelling portion of the Penrose Drain.
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Research and development of the new radiopaque centimeter-calibrated Penrose Drains have been conducted in collaboration with: Dr. Donald F. McDonald, Chief of Urology, Strong Memorial Hospital; Professor of Urology, University of Rochester School of Medicine and Dentistry, Rochester, N. Y. Dr. Walter J. Pories, Department of Surgery, Strong Memorial Hospital, Rochester, N. Y.



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Dulcolax Dulcolax Disactivity Tablets and suppositories

the laxative with a bibliography



The extensive bibliography* on Dulcolax, amounting to almost 100 clinical reports, strongly affirms its clinical advantages.

Induces Natural Evacuation

The action of Dulcolax is based on simple reflex production of large bowel peristals on contact with the colonic mucosa. As a result, stools are usually soft and well formed and purgation is avoided.

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With Dulcolax tablets action is almost invariably obtained overnight...with suppositories action occurs within the hour.

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Dulcolax is as well adapted to preparation for radiographic and operative procedures as it is to the treatment of constipation.

*Detailed literature, including complete bibliography, available on request.

Dulcolax®, brand of bisacodyl: Tablets of 5 mg. and suppositories of 10 mg. Under license from C. H. Boehringer Sohn, Ingelheim.

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Proven

in over six years of clinical use and more than 750 published clinical studies

Effective

for relief of anxiety and tension

Outstandingly Safe

- 1 simple dosage schedule produces rapid, dependable tranquilization without unpredictable excitation
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Miltown

Usual dosage: One or two 400 mg. tablets t.i.d. Supplied: 400 mg. scored tablets, 200 mg. sugar-coated tablets; in bottles of 50.

Also supplied in sustained-release capsules . .

Meprospan^o

Available as Meprospan-400 (blue-topped sustainedrelease capsules containing 400 mg. meprobamate), and Meprospan-200 (yellow-topped sustained-release

capsules containing 200 mg. meprobamate).

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May, 1961

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Page 49



how shall she dress she wants to know now you can tell her (even in the first week)



Pro-Duosterone

anhydrohydroxyprogesterone, 50 mg. $\}$ per tablet ethinyl estradiol, 0.03 mg. $\}$

the 3-day, oral test for early diagnosis of pregnancy

If she is not pregnant, and has previously had regular menstrual cycles, withdrawal bleeding will occur within a few days after PRO-DUOSTERONE (1 tablet q.i.d. for 3 days). In functional amenorrhea, regular cycles are often restored.

If she is pregnant, no progesterone withdrawal bleeding can occur. Pro-Duosterone actually protects pregnancy, and may be indicated to

help improve implantation in habitual abortion.

"... a safe, physiologic method ...", the convenient Pro-Duosterone test has proved highly accurate (95.2% in 1,553 clinical studies) as early as a week after the first missed menses when animal tests cannot be considered valid. Supplied: Bottles of 24 tablets.

1. Hayden, G.E.: Am. J. Obst. & Gynec. 76:271, 1958.

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The Pregnant

- and a <u>natural</u> way to meet her special need for calcium
- with low-calorie Carnation Instant

Drinking enough milk during pregnancy to assure sufficient calcium has posed the problem of unwanted fat calories — till recently.

Now a natural way to help assure your patients' good calcium and nutritional status is the excellent new food — new Carnation Instant Nonfat Dry Milk mixed 25% overstrength.

One-third cup extra crystals per liquid quart when mixing provides 25% more cal-

cium, protein, and B-vitamins than ordinary nonfat milk. Because your patients can add

this additional amount of Carnation Instant Nonfat, they get needed nutrition—without excessive calories. It's richer, more delicious flavor is a natural way to extra nutrition they will enjoy. Costs them only 12¢ a quart.



ANOTHER QUALITY PRODUCT OF CARNATION COMPANY, LOS ANGELES 36, CALIFORNIA



Why physicians are turning to KORO-FLEX—the arcing contraceptive diaphragm of choice

- 1. Reduces fitting and instructing time.
- 2. Patient ease of insertion-automatic placement.
- 3. Develops patients' confidence. Easy to use.
- 4. Folds behind pubic bone with suction-like action, forming an effective barrier.
- Locks in spermicidal lubricant—delivers it directly under and next to the os uteri.
- May be used where ordinary coil-spring and flat rim diaphragms are indicated.

Recommend: KORO-FLEX Compact, the ONLY compact that provides the arcing diaphragm (60-95 mm) and Koromex jelly and cream (trial size). More satisfied patients result from trying both and then selecting the one best suited to physiological requirements. Eliminates guessing. Supplied in feminine clutch-style bag with zipper closure. Write for literature.

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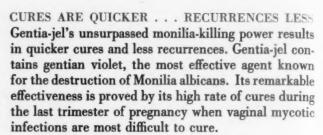
in monilial vaginitis start therapy with the true specific

gentia-jel
it works when others fail



- QUICKER CURES AND LESS RECURRENCES
- . FAST RELIEF OF VULVAR ITCHING AND BURNING
- . SPECIAL DISPOSABLE APPLICATORS PREVENT REINFECTION

In Monilial
Vaginitis
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other therapies
fail...start your
patients with
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FAST, GRATIFYING RELIEF OF VULVAR ITCHING AND BURNING. This soothing jel provides fast relief of vulvar itching and burning. This all important relief is often much faster than that provided by solid dosage forms such as tablets and suppositories.

DISPERSES AND PENETRATES INTO ALL FOLDS. Gentia-jel disperses completely over vaginal and cervical mucosa, penetrates into all folds and bathes the vulvar labia to destroy fungi and bacteria.

SPECIAL DISPOSABLE APPLICATORS PREVENT REINFECTION. Gentia-jel's applicators, unlike many, are never reused, they are discarded...eliminating a major cause of reinfection. The disposable applicators are more esthetic to the patient... and greatly appreciated.

EASIER FOR YOUR PATIENTS TO USE. (1) At bedtime, patient lies back with knees flexed, inserts applicator and instills Gentia-jel. (2) Applicator is removed and discarded and a vaginal tampon or pledget of cotton is inserted in the introitus. A sanitary pad should be worn.

YOUR PRESCRIPTION SHOULD BE FOR TWELVE. Treatment should be continued over 12 days to assure a negative smear.

Gentia-jel is supplied in packages of 12 single-dose disposable applicators. Contains: gentian violet 0.1%; lactic acid 3%; acetic acid 1.0%; in a water-soluble polyethylene glycol base.



the true specific for monilial vaginitis



HELP YOUR PATIENTS HOLD HARD-WON WEIGHT LOSSES



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Although the anorectic effect of many drugs and use of diet substitutes can bring dramatic weight losses, they cannot control the psychic trauma which soon discourages the patient after the first few weeks. Helping patients adjust effectively to the loss of overeating enjoyment requires time and continuing physician-encouragement. Proper supportive medication should offer anorectic action as well as "moral support." Your prescription for Ambar, for example, will provide effective appetite suppression as well as therapeutic action to allay the symptoms of food withdrawal. Ambar will help your patients accept your reducing plan more enthusiastically, and will allow your patients enough time to establish strongly the desirable and needed habit-of-eating-less.

AMBAR, a valuable adjunct in long-term weight control

In a clinical study by Barnes¹ Ambar proved to be a valuable long-term adjunct: "... during the period of observation from 4 to 32 weeks, 44 of the 50 patients lost a total of 800 lbs., or 18 lbs. per patient with a maximum of 65 lbs. in one patient. The average weight loss per week with these patients was 1.16 lb."

Of the conclusions and results of a study by Simkin and Wallace,² the authors state: "The value of a methamphetamine-phenobarbital anorexic agent (Ambar) was evaluated in 101 patients by the single-blind and double-blind method. The over-all loss of weight achieved by patients taking the active medication was significantly greater in both the

double-blind and single-blind groups than that achieved by patients on placebo medication."

"The greatest effect of drug therapy was observed from the 5th to 16th week of therapy, after psychogenic influences had largely ceased to influence the degree of weight loss."

Patients on Ambar lost an average of 1.2 pound per week throughout the 16-week period.

Seven reasons why

should have a place in your weight reduction program

1. Suppresses appetite effectively.

2. Offsets the emotional symptoms of food withdrawal. An optimal methamphetamine-phenobarbital ratio allays anxiety, irritability, overexcitement, as well as fatigue, hunger, depression and lack of energy; encouraging a more favorable doctor-patient relationship.

3. Cardiovascular side effects are minimal—even in hypertensives.

4. Permits "personalized" therapy with 3 dosage strengths.

5. Recommended for the moderately overweight and the "obesity-prone."

Added safety of smooth "Extentab" release no jolts or sudden letdowns.

7. Economical; available on Rx only.

EXTENTABS® PROVIDE 10-12 HOURS OF AMBAR ACTION IN ONE CONTROLLED-RELEASE, EXTENDED ACTION TABLET

DOSAGE AND SUPPLY: AMBAR #2 EXTENTABS#: In each orange Extentab, methamphetamine hydrochloride 15 mg., phenobarbital 64.8 mg. (1 gr.)—one before breakfast, AMBAR #1 EXTENTABS: In each yellow Extentab, methamphetamine hydrochloride 10.0 mg., phenobarbital 64.8 mg. (1 gr.)—one before breakfast, AMBAR TABLETS: In each yellow tablet, methamphetamine hydrochloride 3.33 mg., phenobarbital 21.6 mg. (½ gr.)—one or two before breakfast and lunch and in midafternoon, ~

PRECAUTIONS: While no increase in blood pressure has been reported, patients with cardiovascular disease should be under observation until their response to Ambar is established. Phenobarbital, in excessive and prolonged usage, may be habit forming.

REFERENCES: 1. Barnes, R. H.: Northwest Med. 57:1011, 1958. 2. Simkin, B., and Wallace, L.: Am. J. M. Sc. 239:533-537, 1960.

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AN INSTRUMENT TO DETERMINE CERVICAL COMPETENCY

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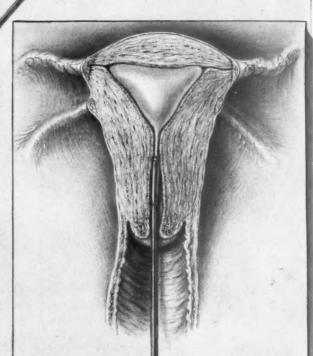


Illustration shows neck of balloon in isthmus and on injection, how the balloon distends first and fills the uterine cavity.

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INDICATIONS: vulvitis/anogenital pruritus/anal and perineal wounds/hemorrhoids/diaper dermatitis/nipple care/minor

TRIAMEL: As Triamel Ointment or Triamel Cream supplied in 2 ounce tubes, with rectal applicator.



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Menopausal Patients are Pleased with ESTROSED® Therapy

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- Vasomotor instabilities respond to ethinyl estradiol,
 ... one of the most potent estrogens known."¹
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Your results with Estrosed therapy will be gratifying. Estrosed contains 0.01 mg. ethinyl estradiol and 0.1 mg. reserpine.

Low Dosage - Economical Therapy

Suggested dosage: One tablet three times daily until symptoms are controlled. Thereafter reduce to maintenance dosage of one tablet every day or two, as may be required.

1. N.N.R., 1959, 515; 2. Ibid., 376

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CONTRAINDICATIONS: In patients with history of mental depression, peptic ulcer, or ulcerative colitis, reserpine in maintenance doses greater than 0.25 mg. daily is contraindicated and smaller doses should be used with great caution. Reserpine should be discontinued 2 weeks prior to elective surgery. In case of emergency surgery, a vagal blocking drug should be given to counteract the potentiation of the hypotensive effect of reserpine by certain anesthetic agents.

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Master craftsmanship, traditional with RAMSES for almost a half century, stands behind the superb quality of every RAMSES Diaphragm—both the regular and the new BENDEX, an arc-ing spring diaphragm.

Quality and design make these RAMSES Diaphragms first choice of your women patients who appreciate elegance and comfort, along with known reliability.



Ramses
Flexible Cushioned
Diaphragm

The regular RAMSES Diaphragm, suitable for most women, is constructed of pure gum rubber, with a dome that is unusually light and velvet smooth. The rim, encased in soft rubber, is flexible in all planes, permitting complete freedom of motion.

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For those women who prefer or require an arc-ing type diaphragm, the new RAMSES BENDEX embodies the superior features of the regular RAMSES plus the very best hinge mechanism contained in any arc-ing diaphragm.

RAMSES "TUK-A-WAY" Kit #701—Designed like a fine accessory, this complete unit contains regular RAMSES Diaphragm 50 to 95 mm., with Introducer and 3 oz. tube RAMSES Vaginal Jelly. RAMSES "TUK-A-WAY" Kit #703—The same complete BENDEX unit minus Introducer (not required with arc-ing diaphragm). Sizes 65 to 90 mm.

Ramses "10-HOUR" Vaginal Jelly *
specifically for use
with Ramses Diaphragms

*Active agent, dodecaethyleneglycol monolaurate 5% in a base of long-lasting barrier effectiveness.

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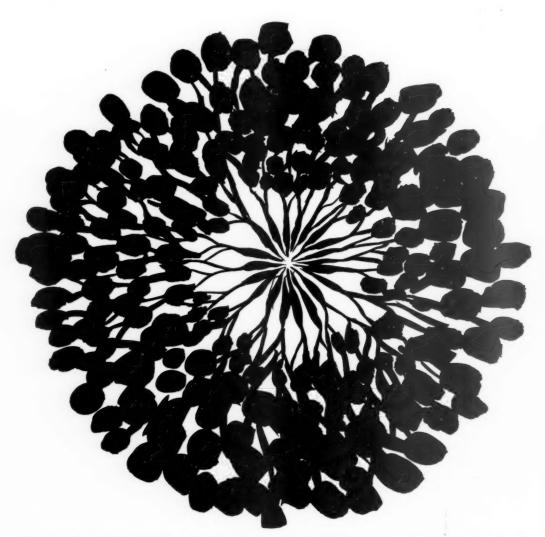
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DELADUMONE 2X

Squibb Testosterone Enanthate and Estradiol Valerate

PREVENTS LACTATION AND BREAST ENGORGEMENT / just one injection at the end of the first stage of labor / optimally balanced, long-acting combination of gonadal steroids for easy injection through small-gauge needle because of low viscosity / virtually eliminates need for analgesics / essentially eliminates withdrawal reaction and secondary breast engorgement sometimes associated with oral medication / does not affect involution of uterus or restoration of normal ovarian function 2.

SQUIBB Squibb Quality—the Priceless Ingredient
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Supply: Each cc. of Deladumone 2X provides 180 mg. testosterone enanthate and 8 mg. estradiol valerate dissolved in sesame oil. Vials of 2 cc. Dosage: 2 cc. given as a single intramuscular injection preferably at the end of the first stage of labor or else immediately upon delivery. For full information see your Squibb Product Reference or Product Brief. References: 1.Watrous, J. B., Jr., et al.: J.A.M.A. 169: 246 (Jan. 17) 1959. 2. Lo Presto, B., and Caypinar, E.Y.: J.A.M.A. 169: 250 (Jan. 17) 1959.





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full term fetus

complication:

threatened abortion

Provera

Here are five reasons why:

- Provera is the only commercially-available oral progestational agent that will maintain pregnancy in critical tests in ovariectomized animals.
- It is four times as potent (by castrate assay) as any other progestational agent.
- · No significant side effects have been encountered.
- It is available for both oral and parenteral administration
- Provera gives the economy of effective action from small doses.

Brief Basic Information

Oral Provera*

Depo-Provera**

Description	Upjohn brand of medroxy- progesterone acetate.	Aqueous suspension, 50 mg. Provera per cc., for intramuscu- lar injection only.	
indications	Threatened and habitual abortion, infertility, dys- menorrhea, secondary amenorrhea, premen- strual tension, functional uterine bleeding.	Threatened and ha- bitual abortion, en- dometriosis.	
Threatened abortion	10 to 30 mg. daily until acute symptoms subside.	50 mg. I. M. dail while symptoms are present, followed by 50 mg. week! through 1st trimes ter, or until fets viability is evident	
Habitual abortion 1st trim.	10 mg. daily.	50 mg. I.M. weekly.	
2nd trim.	20 mg. daily.	100 mg. I.M. q. 2 wks.	
3rd trim.	40 mg. daily, through 8th month.	100 mg. I.M. q. 2 wks. through 8th month.	
Supplied:	2.5 mg. scored, pink tab- lets, bottles of 25; 10 mg. scored, white tab- lets, bottles of 25 and	Sterile aqueous sus- pension for intra- muscular use only 50 mg. per cc., it	

Precautions: Clinically, Provera is well tolerated. No significant untoward effects have been reported, Animal studies show that Provera possesses adrencorticoid-like activity. While such adreno-corticoid action has not been observed in human subjects, patients receiving large doses of Provera continuously for prolonged periods should be observed closely. Likewise, large doses of Provera have been found to produce some Instances of female fetal mascullnization in animals. Although this has not occurred in human beligs, the possibility of such an effect, particularly with large doses over a long period of time, should be considered.

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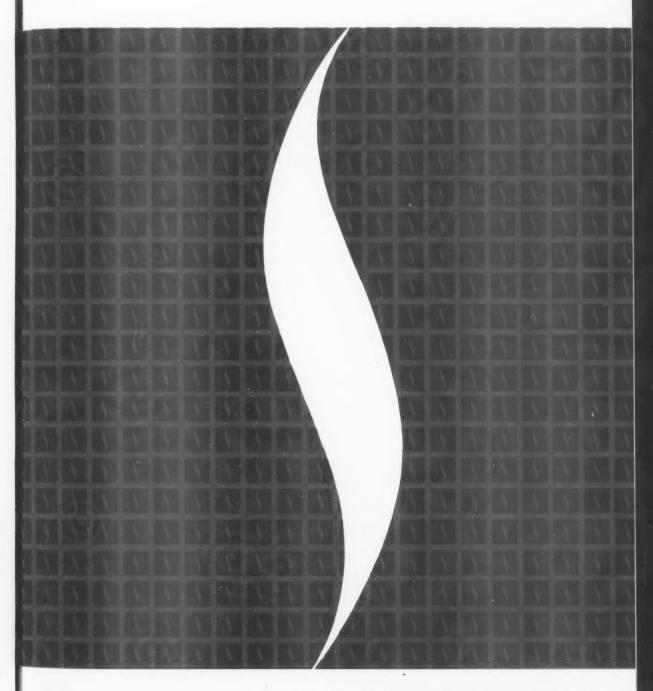
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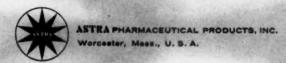
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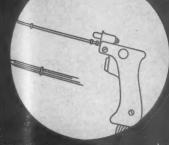
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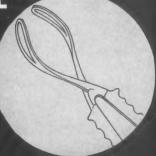




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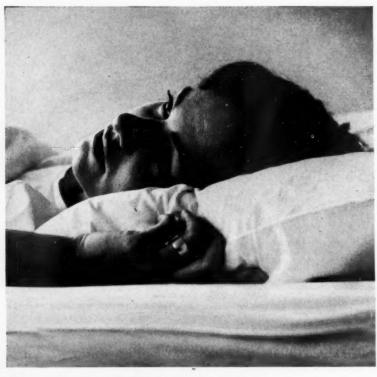
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*Results of a survey of over 1,000 physicians conducted by the Bureau of Research, Inc., 555 W. Jackson Blvd., Chicago 6, Illinois (April, 1960).

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References: (1) Kuntze, C. D.: J. Mississippi M. A. 1:643-644 (Dec.) 1960. (2) Napp, E. E., and Donnenfeld, A. M.: J. Am. Geriatrics Soc. 8:858-860 (Nov.) 1960. (3) Lamphier, T. A., and Lyman, F. L.: J. Internat. Coll. Surgeons 31:420-423 (April) 1959.

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after eleven million treatment courses... consistently broad antibacterial action

Fund of nitrofurantoin through the years...consistently broad antibacterial action against urinary tract pathogens—"It was interesting

to observe that nitrofurantoin [FURADANTIN] showed a consistent in vitro effectiveness against the bacteria tested throughout the four year period, thus revealing negligible development of bacterial resistance, if any, through the years." Jolliff, C. R., et al.: Antibiot. Chemother. (Wash.) 10:694, 1960.

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rapid, safe control of infection throughout the urinary system

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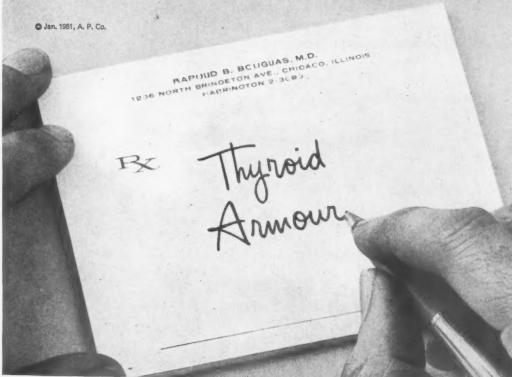
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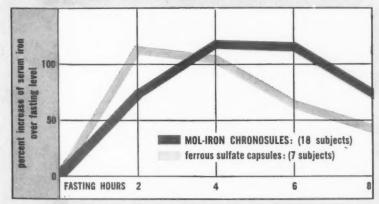
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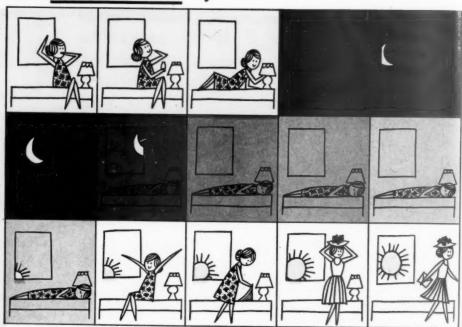
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at bedtime ?



prevents morning sickness here! "...I have gained the best results with [Bendectin]...Because these tablets have a protective coating...the dose taken at night becomes effective in the morning."

NEW DOUBLE-BLIND STUDY SHOWS BENDECTIN EFFECTIVE IN 94% OF PATIENTS²

Medication	Number of patients	Complete relief	Partial relief	Failure
Bendectin	52	23 (44%)	26 (50%)	3 (6%)
		TOTA	L 94%	BEAU
Placebo	57	13 (23%)	24 (42%)	20 (35%)
		TOTA	L 65%	C. 100

"Bendectin was administered in a preliminary study to 146 patients and later, in a controlled, double-blind study to 52 patients, or to a total of 198 patients suffering from nausea and vomiting of pregnancy. A very gratifying therapeutic response was obtained in 178 or 90 per cent. In a double-blind portion of this study, the response of 52 patients treated with Bendectin was compared with that of 57 other patients treated with a placebo. In this group of 109 patients, there was a favorable response to Bendectin in 94 per cent and to the placebo in only 65 per cent."²

Measure Bendectin against your present Rx:

- Q. Has your present Rx been shown to relieve morning sickness before it starts in more than 9 out of 10 patients?²⁻⁵
- Q. Is your present Rx free of phenothiazine-like side effects and habituating properties?
- Q. Is it economical? Does it cost less per day, for example, than a quart of milk?

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Each white, specially coated tablet contains:

Bentyl (dicyclomine) hydrochloride 10 mg.

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DOSAGE: Two tablets at bedtime.

SUPPLY: Bottles of 100 and 500.

1. Middleton, T. F.: Postgrad. Med. #4:699, 1958.

2. Geiger, C. J., et al.: Obst. & Gynec. 5:688, 1959.

3. Nulsen, R. O.: Ohio State M. J. 53:665, 1957.

4. Personal communications, 1956-57.

5. Towne, J. E.: Internat. Rec. Med. 171:583, 1958.

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*Traylor, J. B., and Torpin, R.: Am. J. Obst. & Gynec. 61:71-74 (Jan.) 1951.



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American Journal of Obstetrics and Gynecology

Transactions of the Twenty-eighth Annual Meeting of the Central Association of Obstetricians and Gynecologists

Recipe

President's address

ISADORE DYER, M.D.

New Orleans, Louisiana

IN SEARCHING for an apt subject to present before this association I could not help but be reminded that in the past it has been the intention of many of your presidents to present thoughts relative to the specialty of obstetrics and gynecology, constructive enough to offer improvement for the future. One great example of this was John Brewer's outline that led to the birth of the American College of Obstetricians and Gynecologists. In later years our beloved Herbert Schmitz, of Chicago, suggested means and reasons to combine the training in radiology for the gynecological student who planned to undertake the treatment of cancer in the female. Further emphasis was placed in Axel Arneson's address to this association last year to such an extent that an active committee was formed, its prime objectives being that of furthering and defining proper training in these combined fields.

With these stimuli in mind I have chosen the title, "Recipe." This will not surprise my close friends, I am certain, when one has been accused of being a gourmet, but "recipe" this time is used in a clinical sense. I refer singularly to the recipe for the production of an obstetrician.

The formula throughout the years probably has not changed, but this short discussion is offered this morning for fear that some of its ancient alchemical ingredients may have been overlooked or omitted. Before we can be stimulated to produce something from a formula, we should at least have in mind to some extent the picture of the product for which we strive. In this instance, it is an obstetrician. It is fitting to first ask ourselves, What is an obstetrician?

Less than 30 years ago we would have very little difficulty in pointing out the great obstetricians of the day, such as Joseph Bolivar DeLee, Jennings Litzenberg, and J.

Presented at the Twenty-eighth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Kansas City, Missouri, Oct. 6-8, 1960.

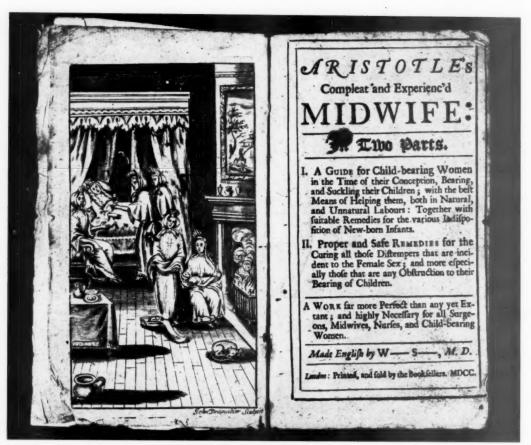


Fig. 1.

Whitridge Williams, to mention three. Their writings, their teachings, their clinical stature were enough that on even casual contact there was no doubt but that they were great clinicians, eccentricities notwithstanding. Because of their efforts and the endeavors of others, many of whom I have not time to mention, a precipitous drop in the maternal and infant death rates occurred. Students influenced and trained by these leaders infiltrated other areas in the country, ever maintaining the integrity and identification of the specialty. Few, if any, of men so influenced have deviated to this date from the rigid adages and principles that were so imprinted upon their natures.

As the past 30 years have gone by we have seen many changes in the practice of obstetrics, brought about in some instances by revolutionary alterations. One of the major

improvements, no doubt, was the transfer of the delivery site from the home to wellequipped hospitals-from deliveries by untrained personnel to deliveries by individuals who were trained in obstetrics. This, coupled with the never-ending fight over hemorrhage and infection, was responsible for the early drop in maternal and fetal deaths. These recollections are often boring to those of you who are young and were born after the early era; however, when one considers that the maternal death rate 50 years ago was 100 per 10,000 births compared to 6 per 10,000 today, this remarkable change was not brought about easily or by any one individual or factor.

In the annual 1931 booklet of the Charity Hospital in New Orleans¹ the report from the board of administrators stated the following: "There were 29 deaths among y, 1961

Gynec.



Fig. 2.

mothers, or only 1.14%." (Table I). In other words, this, being a great improvement over the previous years, was considered something for which to boast. If the same standards existed today in the same institution, we would lose between 110 and 140 mothers per year, whereas the actual maternal death from all causes, including accidents, will rarely exceed 10. So it might be stated that one of the important ingredients in the make-up of an obstetrician would be that conscious desire to search for every means to further reduce the maternal death rate to a lower "irreducible" minimum.

Childbirth, an ever popular topic of conversation among humans of every age, is often a target for numerous articles in lay journals. Today, one of the most popular subjects is the fad, "natural" childbirth. This topic is often presented by some writers

in such a fashion as to imply that obstetricians as a group practice "unnatural" childbirth. If such channels are persuasive enough we are apt to find our patients attending sessions not unlike Yogi, where they are taught to squat and strain and relax and open and shut all apertures in an effort to produce their offspring in a "natural" fearless manner.

I have often been amused by these antics, since the actual theme regarding childbirth without fear is anything but new. This is with full recognition for the late Grantly Dick Reed, who merely brought to light known facts which had been appreciated for many centuries. Proof of this is found in a small volume which I own entitled, Aristotle's Compleat and Experienced Midwife, in two parts, printed in London in 1700, 260 years ago. (Fig. 1). This book, interest-

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ingly enough, belonged to the midwife, presumably Mary Patton (Fig. 2), who delivered the last queen of the Hawaiian Islands, and, after passing through the hands of many families, was given to me by Dr. Robert Hunter, of Honolulu. A quotation from this book is shown in Fig. 3.

Complete avoidance of all types of anesthesia and/or procedures to protect the visible and *invisible* birth canal tears, to say nothing of the effects on the baby whose head must be the foremost extremity of the "battering-ram" is insanity. Complete adherence to producing babies in the raw can only lead to unnatural women physically from the waist down, to say nothing of the baby.

The one objection to this fad would be that of transferring the very important period of emotional conditioning from that of the obstetrician to some outside party whose ultimate influence may be absent at the time of actual labor. Not very long ago such a class in exercises was inaugurated in our city and many of my patients inquired as to whether or not they could attend. Having no serious objection I permitted a few to attend these classes, only to find out some months later that the nurse conducting the classes was a woman who had had four babies by cesarean section and who in substance had never actually experienced labor. This immediately reminded me of some women who visited our area in northeastern Oklahoma before the war and lectured to the local Parent-Teachers Association groups on the necessity of breast feeding. Invariably the ardent lecturers were flat-chested, unmarried social workers. I say this to emphasize the point that the motives for the advocates of such fads should certainly be investigated.

The justification for such efforts to instruct prenatal patients will not be found in areas wherein the obstetrician instinctively instills emotional security in the young women under his care. Fads are unnecessary ingredients in this recipe.

It should never be said that obstetricians are not in favor of making a delivery as pain-

Table I. Causes of death of 29 mothers at Charity Hospital in New Orleans, 1931

Eclampsia			3
Nephritis			3
Shock (rupture, placents	a previa,		
separation of placenta	,		
deformed pelvis)			6
Organic heart disease			2
Hemorrhage			5
Pulmonary embolism			2
Pneumonia			3
Pulmonary congestion			1
Septicemia			2
Typhoid fever			2
Meningitis			1
Toxemia			1
No. of children born		2,566	
Males	1,306		
Females	1,260		
Delivered living	2.395		
Stillborn	171		

less an event as possible for the parturient. This has been the objective for centuries. It has been within our time that the sudden and rapid development of all types of drugs and the dissemination of knowledge of these drugs through word-of-mouth and in the lay press, to say nothing of the accepted popularity of the times, has inadvertently led some obstetricians into the injudicious use of pain relievers. A well-integrated obstetrician would adhere to the dictum so beautifully stated by the late Roy Calkins on labor, printed in 1955,3 in which the following were emphasized:

1. The obstetrician should be ever mindful of the fact that every anesthetic is a poison to the baby.

Do not use a drug with which you are not thoroughly familiar.

3. More important than knowing the drug is knowing the dose of that drug.

4. No matter what drug or anesthetic used it is obligatory on the attendant to maintain a constant watch on the effects of such on both the mother and baby.

Reports have been received through the literature of women who have suffered gargene and loss of digits (one or more fingers from the hand) as a direct result of introvenous drugs administered in labor. This, I believe everyone here will admit, is a very high price for a mother to pay for the

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privilege of bringing a baby into the world. Furthermore, the mere fact that it will appear necessary in the minds of some to render women unconscious throughout their labor and delivery is a direct admission of total inability on the part of the obstetrician to have established any rapport with his patient, his total ineptness in establishing any degree of emotional discipline in his patient, and a glaring admission that he does not have the welfare of the mother and her baby at heart. The same may be said of those practitioners who plan mass inductions of labor for their convenience on specific days of the week. Both habits should never enter this recipe.

In the teaching of obstetrics 30 years ago the subject enjoyed a prominent place in the curriculum, with enough time allotted in order to impart some sense of appreciation in the minds of medical students. Present-day curricula are so crowded with the increase in other subjects demanding teaching hours that we now find obstetrics slowly doomed to almost as diminished an amount of time as was previously allotted the minor surgical specialties. Yet the majority of students will deliver babies and many practice obstetrics for the rest of their lives, which cannot be said of the application of

many other medical school subjects taught them.

The embarrassment is further enhanced by the recent marriage with gynecology in an effort to save her from the clutches of general surgery. It has become necessary, and rightly so, to bring the specialty of gynecology to the forefront in order to preserve its identity. The emphasis, however, has permitted the training of residents who could, after 3 years of excellent supervision, become cancer surgeons superior to any men of their age in the country, yet could be totally devoid of any appreciation of the true art of operative obstetrics, to say nothing of their ability to handle the emotional problems of women they will see for the rest of their lives in the practice of obstetrics. Under the guise of the combined specialties they could continue to deliver women begrudgingly, purely because of the necessity of using this medium to feed gynecological surgery into their offices.

Let it not be misconstrued that in the recipe of an ideal obstetrician knowledge of gynecology, endocrinology, and adeptness in gynecological surgery is not a necessity. This is true. It is *not* true, however, that the thorough knowledge of gynecology and gynecological techniques automatically equips one as an obstetrician in the true sense.

The realm of obstetrics still contains horizons which should be a great challenge to the young trainee. Much is still unknown in regard to fetal physiology in utero, to say nothing of the many roles and peculiarities of the placenta. The actual true motivation for the onset of labor still remains a puzzle. It therefore rests with the ideal obstetrician to also have some curiosity in regard to the unknowns; to busy himself in some research and to keep thoroughly informed with the research of others. He should always appreciate the one fact that if today we can see farther than others, it is because we stand upon the shoulders of giants, always appreciating that the picture as we see it today was once a puzzle which was slowly put together, piece by piece, laboriously, by those who went before us.

Some Women there are who protract their Delivery, by reason of their Shamefac'dness or Modesty; as not being willing their private Parts shou'd be expos'd to the view of some Persons that may be at that time there; and in such a Case, the Persons who are the Cause thereof, must be desir'd to quit the Room, Others protract the Birth, by reason of their Timidi-ry, and extream Fear of some farther Pain than what the at present feels; tuch must be advised, that it is the Will of the Author of our Beings that it should be so; and that her Fears are beyond what she will feel; and that others have gone through greater Pains than she is like to have : Such comfortable Words being oft-times a great Support to the labouring Woman. If she be melancholy, (for sometimes difficult Labour arises from thence) endeavour by all means to make her chearful; and encourage her to believe, that all will soon be over, and that she shall have such a Child as the defires: That her Sorrows will be foon turn'd into Joy, and that she is in no danger; especially when danger is not very evident.

Speaking of research, recently at a meeting of the North Dakota Society of Obstetrics and Gynecology, I was impressed by two serious research scholars with whom I shared the program. At the conclusion of the meeting I could not help remarking how refreshing it was to note that with one devoted to the endocrine aspects of ovulation and the endometrium, the other to fertilization of rabbit ova and implantations, like insecticides and roaches we could stay ahead of the contraceptive pill and still stay in business.

In March of this year at the conclusion of a final examination in obstetrics for senior medical students I asked one question: to list 10 attributes necessary in the make-up of an ideal obstetrician. The following answers are interesting to note what senior medical students think. For example:

- 1. He should be an intelligent person.
- 2. He must be an emotionally mature, well-adjusted, happy individual who sincerely loves people, life, and medicine.
- 3. He must be interested in the patient's welfare.
- Have an understanding, cooperative wife.
- 5. Think for himself and not let other physicians tell him how to handle the delivery.
 - A decent surgeon.
- 7. The ability to stand a lifetime of women patients.
- 8. Sufficiently handsome to satisfy female ego in herself and "her" doctor.
- Ought to be particularly fond of women (all kinds, almost) and understand their mental make-up.
- 10. He also needs a wife who has at least one baby.

And then one enterprising student wrote the following: "He must be persistent (never lose hope)." Then he quoted Napoleon in French (Fig. 4).

The recipe can include, then, some of the attributes suggested by the students.

One may wonder, then, how we can accomplish such aims. Not many years ago, in the summer of 1952, one of our members, George H. Gardner, of Northwestern Uni-

versity Medical School, in his departmental report, had the following to say:

Finally, the Department of Obstetrics and Gynecology at Northwestern University HAS TWO GLARING SHORTCOMINGS, over and above its profound need for an adequate endowment; I strongly suspect that if we could overcome one of them the others would be solved rather promptly. Our greatest need is to develop or import, dyed-in-the-wool, younger obstetricians. I refer to men who live, breathe, and think ONLY about obstetrics; and men who are vitally concerned with the teaching of obstetrics, and with obstetrical research; and men who are endowed with such zeal for their specialty that they will instill similar enthusiasm into their students, into their house officers, and into their younger associates. This department, at present, is top-heavy with men who constantly effervesce about gynecology. We need MEN OF THE SAME TYPE in obstetrics.

The sentiments expressed could not be more explicit, and I suggest that this organization go on record to sponsor the development of obstetricians in medical schools, who for their fourth or fifth year of residency training will concern themselves chiefly with the indoctrination of house staff and medical students. They should be omnipresent, both in the schools and in the delivery rooms to practice what they preach. This would require long hours and necessarily demand a missionary spirit.

How important this would be to enhance the thousands upon thousands of dollars that are being spent today in the investiga-



Fig. 4.

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THE PHYSICIAN

WHEN the final history of the world is written, the physician will stand alone in the variety of his economic usefulness, his field apart, yet touching at all times the toga of the citizen, the robe of the priest, the periwig of the advocate, the scarlet of the judge, the mask of the executioner-each shadowing his life with the mixt bitterness of reproach at the limitations of his ability in the midst of so great a field of labor and of so large possibilities of accomplishment, while always the whisper of the succored child, the prayers of the convalescent and the glory in sharing the salvation bring the ray of light which lends the soft harmony of gentleness which should be the signal standard of the true physician, as, at the end, he stands a sad and thoughtful actor in the Human Comedy.

New Orleans, 1910

Isadore Dyer, M.D.

Fig. 5.

tions in cerebral palsy! I would venture a guess that cerebral palsy would show a decline in practice today if the over-all quality of obstetrical delivery care was improved.

The quality of the clinician can be theoretically measured in his intelligence, his type of training, his moral fiber, and, most of all, his clinical experience, as well as his ability to recall. In monitoring a very large charity service, as well as three hospitals out of town, together with a private practice experience, I am in contact with the abnormalities occurring in approximately 16,000 to 18,000 deliveries per year. With these experiences, hardly a month will pass but that some obstetrical problem will be presented, the likes of which had not occurred previously in our experiences. The end results for both the mother and baby will then depend upon the rapidity with which decisions are nade, as well as the response on the part of the patient.

Should the end result prove unfavorable, the cause may be due to poor patient reponse, previous physical condition, the element of time, the ability to sustain shock, the patient's ability to recuperate, her intrinsic defenses against infection, and the nebulous *inherited* qualities of the delivered product, to mention but a few.

The conclusion drawn in an article written for the Journal of the Michigan State Medical Society in December, 1955,⁵ in regard to the management of the primigravid woman, should be included in the recipe for the objectives for the ideal obstetrician, as follows:

In conclusion, let me emphasize that obstetric management of the primigravid woman is a challenge to the obstetrician. He holds the key to her happiness and to her future. Success in any maternity should not be measured in statistics alone, but in terms of live, unharmed babies, whose mothers are physically sound following their experience in childbirth, and emotionally secure, with a genuine desire to repeat the performance again and again.

With poetic license, I cannot let this day go by without at least mentioning the one individual who has influenced my thinking perhaps more than any person who ever lived. I refer to my father, Isadore Dyer, Dean of the Tulane Medical School and Professor of Dermatology, who, among many accomplishments, founded the Leprosarium at Carville. He was an international authority on leprosy. At the end of a little book of essays⁶ he composed a short paragraph entitled, "The Physician" (Fig. 5).

This should also enter the recipe in the life and trials of the ideal obstetrician, for, after all, he is primarily a physician. We should save that recipe and prevent any of the ingredients from being substituted, altered, or deleted. This association must preserve his identity for posterity.

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Fig. 4.

Use of proteolytic enzymes in surgical complications, obstetrics, and gynecology

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THIS paper reports our clinical experience with proteolytic enzymes as débriding agents as well as certain in vitro studies with these enzymes. Initially fibrinolysin was used alone and this was reported. More recently a combination of fibrinolysin and desoxyribonuclease* was investigated.

A historical review of these proteolytic enzymes will serve as background information for later discussion in this paper.

Fibrinolysin

In 1893 Dastre² discussed a proteolytic substance in blood serum capable of lysing blood clots and proposed the name "fibrinolysin" for the active substance. In 1903 Delezenne and Pozerski³ found the proteolytic activity of serum to be augmented by chloroform extraction. This observation has been confirmed by others.⁴⁻⁷ Astrup,⁸ and Sherry and co-workers⁹ have "written reviews of recent studies on fibrinolysin.

Fibrinolysin was isolated in 1946 in purified form by Loomis and associates.¹⁰ This

enzyme was isolated from bovine plasma and activated by chloroform. Bovine fibrinolysin is a water insoluble, saline soluble, and nondialyzable euglobulin with an isoelectric point at pH 5.5. The Loomis unit of fibrinolysin was used in this study.¹⁰

Bovine fibrinolysin may be antigenic in humans; an anaphylactoid reaction may occur after repeated injections. Fibrinolysin has general proteolytic activity, but it acts primarily to produce relatively large, soluble, split products of proteins. It hydrolyzes these split products at a much slower rate than trypsin or other proteases. Fibrinolysin hydrolyzes plasma proteins other than fibrin in vitro; however, it is believed that in vivo plasma proteins are substantially protected by the preferential binding of fibrinolysin with antifibrinolysin.

In the dry state fibrinolysin is very stable. In solution it is less stable and loses enzymatic activity in 6 to 8 hours at room temperature, or after several days at 3° C.

Desoxyribonuclease

Desoxyribonuclease is a nucleolytic enzyme isolated in purified form from the bovine pancreas. The method of isolation was described by Kunitz.¹³ This pancreatic desoxyribonuclease is a small, water-soluble protein with a molecular weight of about 60,000 and an isoelectric point near 5. The enzyme is activated by bivalent cations, provided by tissue fluids. Its op-

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*Elase, Parke, Davis & Company registered trademark for fibrinolysin-desoxyribonuclease combination.

timal activity is at pH 7. The lyophilized form is stable for an indefinite period of time. Once dissolved in saline, its activity gradually falls over a period of days at a temperature of 5° C. More rapid deterioration occurs at higher temperatures. A unit of desoxyribonuclease is defined by Christensen.¹⁴

Pancreatic desoxyribonuclease catalyzes the hydrolytic fission of certain internal bonds in the large molecules of desoxyribonucleic acids, splitting them into smaller fragments; this is demonstrated by the rapid fall in viscosity of solutions of desoxyribonucleic acid. Desoxyribonucleic acid protein complexes are present in abundance in purulent exudates.

Hypothetically, the combination of fibrinolysin and desoxyribonuclease should be more effective than fibrinolysin alone in promoting the dissolution of undesirable exudates on body surfaces and mucous membranes, thereby enhancing the normal process of healing. Fibrinolysin breaks up the fibrin component of the exudate, and desoxyribonuclease breaks up the desoxyribonucleic acid component.

Mammalian blood contains a proenzyme "profibrinolysin" or "plasminogen" which is fibrinolytic after activation. The active enzymes are termed "fibrinolysin" or "plasmin," respectively. There are species-specific differences in ease of activation of these enzymes; the bovine proenzyme is more easily activated than the human. Various substances may be used as activators; one of these, streptokinase, a substance derived from cultures of Lancefield Group A streptococcus, has been used to activate the plasminogen present in wound debris; it has no innate proteolytic activity.

Materials

Materials for our studies consisted of the following: For the first study, (1) lyophilized powder supplied in vials, each containing 50 Loomis units per vial of bovine fibrinolysin activated by chloroform to be reconstituted with saline; (2) lyophilized powder supplied in vials, each containing 100

Table I. Demonstration of compatibility of fibrinolysin and desoxyribonuclease with various antibiotics

Antibiotic	Concentration 0.6 and 1.2 Loomis units per ml.	Recovery of lytic activity (%)	
Penicillin	500 units	100	
Chloramphenicol	0.25 mg.	100	
Streptomycin	1.00 mg.	100	
Achromycin*	0.20 mg.	100	

*Required adjustment of media to pH 7.

Loomis units per vial of bovine fibrinolysin activated by chloroform to be reconstituted with saline. For the second study, (1) lyophilized powder supplied in vials, each containing 25 units of fibrinolysin and 15,000 units of desoxyribonuclease to be reconstituted with saline; (2) ointments supplied as 1 ounce tubes, each tube containing 30 units of fibrinolysin and 20,000 units of desoxyribonuclease; and (3) ointments supplied in 1 ounce tubes containing 30 units of fibrinolysin, 20,000 units of desoxyribonuclease, and 0.3 Gm. chloramphenicol.*

In vitro studies

A. Investigation of the compatibility of the enzyme combination with various antibiotics was carried out in vitro as outlined in Table I.

As evident from Table I, no loss of enzymatic activity was observed with the addition of the tested antibiotics.

B. We proposed the hypothesis that the enzyme combination should be effective in the treatment of Trichomonas infestation. To substantiate this contention, we carried out some in vitro studies, which are shown in Table II.

In the concentration of 6.25 units per milliliter, fibrinolysin caused trichomonads to clump and lose motility. The effect was transitory, and the organisms recovered in 24 hours. In the concentration of 12.5 units per milliliter fibrinolysin not only caused the

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^{*}Parke, Davis & Company's registered trademark for chloramphenicol is Chloromycetin.

Table II. Laboratory study of fibrinolysin and desoxyribonuclease on trichomonad culture*

	Time		Condition of	of trichomonads	
Group	interval	Normal	Clumped	Motile	Nonmotile
I	1 hour		x	x	
(12.5 units fibrinolysin)	2 hours		x	Less motile	
	6 hours		Slightly	Very motile	
	24 hours	x			
II	1 hour		x	x	
(25 units fibrinolysin)	2 hours		x	Less motile	
, , ,	6 hours		x	Little motility	
	24 hours		Cleared of all trichomonad		
III	1 hour	x			
15,000 units desoxyribonu-	2 hours		Slightly	x	
clease)	6 hours	x	,		
,	24 hours	x			
IV	1 hour		x	x	
25 units fibrinolysin; 15,000	2 hours		x	Less motile	
units desoxyribonuclease)	6 hours		x	Less motile	
	24 hours		Disintegrating		Single tricho- monad
v	1 hour	x			
(untreated controls)	2 hours	x			
	6 hours	x			
	24 hours	x			

^{*}Test method: test preparations were made by adding the components to 2 ml. undiluted 24 hour trichomonad culture. These preparations were checked for motility and clumping at 1, 2, and 6 hours and then were incubated for 24 hours at 37°C.

Table III. Clinical results of patients treated with fibrinolysin

			71	
	No.	1	Results	
	cases	Good	Fair	Poor
Group I. Liquefaction of blood clots Indications				
Hematomas	19	16		3
Blood clots in genitourinary system	12	7	4	1
Miscellaneous	7		5	2
Total	38			
Group II. Débridement of wounds and draining sinuses				
Postoperative mastectomy wound	9	8	1	
Abscesses	3	3		
Ulcers	8	7		1
Draining sinuses	7	7		
Miscellaneous	5	2		3
Total	32			
Group III. Respiratory complications				
(postoperative)			1	
Atelectasis	24	24		
Tenacious bronchial secretion	6	6		
Total	30			

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trichomonads to clump and lose motility, but lysed them within 24 hours. Desoxyribonuclease, alone or in combination, had no demonstrable effect on trichomonads. No consistent effect on trichomonads could be seen from the enzymes supplied in ointment form.

C. We have exposed human sperm to enzyme combination in vitro and have noted prompt cessation of sperm motility after each exposure. Whether or not this would imply spermicidal action is a question which cannot be answered at this time.

Clinical studies

Previously we reported our experiences with three groups of patients in whom fibrinolysin alone was used. Group I contained 38 patients in whom liquefaction of blood clots following operation or trauma was attempted; Group II consisted of 32 patients, in which débridement of infected wounds and draining sinuses was desired; and Group III comprised 30 patients showing postoperative respiratory complications (Table III).

Methods of application of fibrinolysin, dosage range, and results have been published.¹

Successful treatment in Group I is judged by the amount of liquid blood aspiration and the reduction in size of the hematoma or clot. Although good results were obtained in Groups II and III, these can be considered only as favorable clinical impressions, since control studies were not conducted.

The second division of the study comprises a group of 328 patients who were treated for conditions classified as: (I) débridement of postoperative wounds, (II) abscesses, (III) vaginitis and cervicitis, and (IV) miscellaneous.

Group I. Treatment of patients for débridement of postoperative wounds made use of both liquid (25 units of fibrinolysin and 15,000 units of desoxyribonuclease in lyophilized form reconstituted with normal saline) and ointment as outlined in materials with and without added antibiotic (chloramphenicol).

Ointment with antibiotic was used for 48 hours or longer where "infected" areas persisted. Ointment without antibiotic was then substituted after infection subsided (Table IV).

In all of these cases where débridement of postoperative wounds was considered necessary, the application of enzyme in either liquid or ointment form provided demonstrable good results in terms of: (1) "cleaning" skin exudates in patients with radical mastectomy wounds; (2) "cleaning" wound surface where slough occurred in radical vulvectomy wounds and encouraging early formation of normal granulation tissue; (3) facilitation of healing followdébridement of necrotic particles and seropurulent exudates accumulating between the plastic obturator and the newly created vagina in patients where plastic formation of vagina was performed; and (4) "cleaning" areas and diminishing foul odor and serosanguineous discharge in patients with extensive genital carcinomas in which therapy failed.

Nursing and medical personnel reported that patient care was facilitated in these instances.

Group II. Utilization of both liquid and ointment enzymes in the treatment of patients exhibiting abscesses followed accepted surgical management (Table V).

Following incision and drainage, breast abscesses were either perfused with enzyme solution or a topical application of ointment was made to the surgical wound.

Comparable control cases, similarly managed except for medication with enzyme, were observed.

Enzyme-treated breast abscess wounds showed rapid débridement and early healing as compared to untreated control patients whose wounds drained for a longer period of time.

Other types of wounds treated with enzyme liquid and/or ointment included infected surgical abdominal wounds, post-operative hematomas, and wound dehiscences. Observation of rapid blood clot lysis after instillation of enzyme through a poly-

Table IV. Clinical results of patients treated with the combination of fibrinolysin and desoxyribonuclease

		No.	Type of treatment		
	cases	Ointment	Liquid	Both	
Group I. Débridement of postoperative wounds					
Radical mastectomy		4	2		. 2
Radical vulvectomy (with node dissection)		3		3	
Extensive vulvectomy		2		2	
Plastic formation of vagina		2	1	1	
Débridement of inoperable cancer		3	3		
Total		14			

Table V. Clinical results of patients treated with the combination of fibrinolysin and desoxyribonuclease

	No.	No Type of medication		Results			
	cases	Liquid	Ointment	Both	Good	Fair	Poor
Group II. Abscesses							
Breast abscesses	6			x	6		
Abdominal wound abscesses	5			x	4		1
Pelvic abscesses	2	x			2		
Postoperative hysterectomy-							
cuff abscesses	3		x		2	1	
Total	16						

Table VI. Clinical results of patients treated with the combination of fibrinolysin and desoxyribonuclease

		No. Length of treatment (days)	Results			
			Relief of symptoms	No relief	Recurrence*	
					1 mo.	2 mo.
Group III. Vaginitis and cervicitis						
Trichomonas	50	6	50		- 35	33
Nonspecific vaginitis	48	3-5	48		20	
Cervicitis—postpartum	37	5	35	2		
Cervicitis—postcauterization	28	5-7	28			
Chronic and acute cervicitis	67	5-7	60	7		
Total	230					

*Recurrence by smear and/or culture.

ethylene tube was made, and satisfactory débridement of wound, followed by prompt healing, occurred in each treated patient.

Instillation of enzymes into the pelvic abscesses is not original with us. Collins¹⁵ reported a method of instilling enzymes into the bulging cul-de-sac, after which incision and drainage were performed. We followed the same procedure in our 2 cases. The surgical wound was perfused with the enzyme

through the drainage tubes left in place. Enzyme treatment diminished the viscosity of pus and facilitated drainage. Despite the enzymatic action both patients underwent laparotomies because of the inability of the enzyme to lyse the multiple pus pockets.

Group III. Group III includes patients who had vaginitis and cervicitis and were treated with enzyme ointment (Table VI).

In trichomonas vaginitis, patients treated

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with enzyme ointment nightly for six applications attained symptomatic relief from discharge, itching, burning, irritation, and odor. Repeat cultures and smears one month after a course of treatment showed positive cultures for trichomonads in 35 patients. Two patients had negative cultures after a second course of treatment.

Nonspecific vaginitis, postpartum cervicitis, and acute and chronic cervicitis showed improvement with enzyme ointment medication and complete relief of inflammation and discharge.

Postpartum cervicitis patients treated with enzyme ointment in most cases did not need silver nitrate or cauterization of cervix.

Monilial vaginitis was not cured by enzyme ointment application.

Group IV. Group IV consisted of patients having circumcision or episiotomy wounds which were treated with enzyme ointment (Table VII).

Sixty newborn male infants were circumcised shortly after birth. Thirty circumcision wounds were treated with gauze impregnated with enzyme ointment, the other 30 with standard petroleum jelly gauze. In the 30 treated patients 27 wounds healed quickly and showed no inflammation at the time of the patients' discharge from the hospital on the fourth day. The untreated infants showed penile discharge in 14 of 30 cases.

Eight inflamed episiotomy wounds healed quickly and without odor or discharge when enzyme ointment was applied. No controls were used.

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Certain theoretical concepts in the use of enzymes for débridement may properly be considered at this point. Exact controlled studies in clinical application of an agent for enzymatic débridement are almost impossible to achieve. When alternate managements with enzyme and placebo was possible, this was done. Similar surgical lesions (circumcision) were treated with placebo and compared to equal groups managed with enzymes. We admit that clinical

Table VII. Clinical results of patients treated with combination of fibrinolysin and desoxyribonuclease

		Length of	Results		
	No.	treatment (days)	Good	Slower healing	
Group IV. Miso	ellane	ous			
Circumcision	30	4-6	30		
Control	30	-		30	
Episiotomy	8	1-2	8		
Total	68				

impressions must constitute a major basis of judgment of the efficacy of such treat-

Some investigators¹⁶ believe that lysis of fibrin can be achieved by applying proenzyme activators to necrotic debris. This concept is valid if sufficient profibrinolysin is present and readily accessible within the wound. We agree with Ambrus and his group¹⁶ that improved results will be obtained if the complete activated enzyme is supplied rather than the activator. It is also logical that the addition of desoxyribonuclease to fibrinolysin should enhance the dissolution of necrotic particles.

In the initial part of our investigation, we were impressed with the ability of fibrinolysin to dissolve hematomas, débride wounds, and clean up draining sinuses. It was our impression that postoperative respiratory complications were markedly improved by the inhalation of fibrinolysin; this could suggest that hyaline membrane disease of the newborn may also benefit from this type of therapy.

In the later studies, in which we used combined enzyme therapy, we felt that the results obtained in gynecologic surgery, radical mastectomy, radical vulvectomy, postoperative wound infections, wound dehiscence, and vault abscesses after hysterectomies proved the efficacy of the enzyme and the superiority to other type of management. We were equally impressed with the use of the enzyme combination in office practice for the treatment of cervicitis, and

its utility in nonspecific vaginitis; we were disappointed with its failure in handling trichomonas vaginitis in vivo.

Although the enzymes used are potentially antigenic, we remark that it is notable that no antigenic reactions from this material were observed.

Summary

The combination of fibrinolysin and desoxyribonuclease herein reported has been found to be an effective débriding agent in a wide variety of obstetric and gynecologic conditions, in a variety of surgical complications and in other miscellaneous conditions where necrotic material (infected or noninfected) should be removed.

1. The enzymatic combination of fibrinolysin and desoxyribonuclease is efficient when applied intravaginally, where it promotes the rapid removal of necrotic debris associated with vaginitis and cervicitis as well as clots and tissue debris occurring post partum and following a variety of operative procedures on the cervix uteri.

2. Although symptomatic relief was obtained, the enzyme combination proved to be a failure in the management of trichomonas vaginitis.

3. The enzyme combination was used successfully in irrigating abscess cavities, hematomas, sinus tracts, fistulas, etc., where it helped to remove debris and promote healing. While these beneficial effects of the enzymes alone are evident regardless of the presence of infection, the combination with a broad-spectrum antibiotic augments their efficacy when bacterial infection is associated with the exudate.

We wish to express our gratitude to Dr. J. P. Pratt, Dr. H. Nelson, and Dr. K. Campbell for permission to include their cases in this study.

The fibrinolysin and desoxyribonuclease in this study was kindly supplied by the Department of Clinical Investigation of Parke, Davis & Company, Detroit, Michigan.

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Discussion

DR. PAUL D. BRUNS, Denver, Colorado. In this report the clinical observation of fibrin dissolution has been ascribed to induced fibrinolytic activity following application of the enzymes to purulent wounds, cervical discharges, and vaginal secretions. However, it is not quite clear that this mechanism actually accounts for all the observed effects. In fact the capriciousness of normal behavior, to say nothing of disease states

and infected wounds in particular, could explain variation in healing even though it is unlikely.

Possibly this question might have been answered had use been made of the fibrin plate or other appropriate tests, by checking fibrinolytic activity of the purulent material at regular intervals during treatment. However, as the authors point out, it is very difficult to control experiments of this nature. Separating patients

into groups of "good risk" and "poor risk," maintaining an adequate observation period before therapy, using the double-blind technique, and carrying out complex laboratory tests to demonstrate mechanisms of action are difficult.

It might be much more apropos to congratulate the authors on the large number of patients they successfully treated than to harass them about minor details such as the following questions might pose: (1) are there any data available on the stability of the fibrinolytic enzymes in an ointment medium? (2) It is known that antibiotics do not affect the activity of fibrinolysin-does fibrinolytic activity affect the bacteriostatic power of antibiotics? (3) Is the sperm inactivation with Elase due to (a) fibrinolysin, (b) desoxyribonuclease, or (c) other byproducts of the preparation? (4) A suggestion was made that proteolytic enzymes might be of value in the treatment of hyaline membrane disease-are such studies being done and what are the preliminary results? (5) It is known that bovine fibrinolysin may sensitize a patient to bovine fibrinolysin and to bovine serum-might not skin testing be indicated before therapy especially if re-treatment is contemplated?

Dr. Conrad G. Collins, New Orleans, Louisiana. We began to use enzymatic débridement of abscesses and wounds in 1952, although we use a different product. The origin of the enzymes used is the alpha-beta hemolytic streptococcus which has streptokinase and streptodornase. This was first used by thoracic surgeons in the treatment of hemothorax, and we decided to try it for pelvic abscesses.

In our method, the abscess in the cul-de-sac is tapped, 8 or 10 c.c. of pus is removed, and then the enzyme is injected. The enzyme is allowed to act for 24 hours, and then colpotomy is done.

The pus is put in a standard-sized tube with about an 18 or 20 gauge needle, and then the number of drops obtained from the exudate through the needle per minute is timed. In most cases we obtain pus prior to enzymatic débridement with introduction of the enzymes, and only 4 or 5 drops a minute will come through this needle. The next day, at the time of colpotomy, the pus is again put in the same tube with the same caliber needle, and 15 to 20 drops per minute of pus come through, showing that the viscosity is markedly decreased.

We do not use large drainage tubes any more; rather, small gall bladder tubes are used and in 5 to 7 days the patients are well.

Enzymatic débridement should play a great part in the treatment of pelvic abscesses. We also use it in wound complications, such as Dr. Margulis has described, and we think wound healing is faster than with any combination of antibiotics and other agents.

Dr. Margulis (Closing). The stability of the ointment was tested at 6 month intervals. Beyond that I did not do the testing myself, but relied on the word of Parke, Davis & Company, who make the product. After 6 months the ointment was just as effective as before.

This has not only been a clinical study on patients, but we also did some testing in vitro. As far as the bacterostatic effect of the enzyme combination is concerned, Dr. Connell, of New York, has demonstrated the bacteriostatic effect in culture plates (Surgery 47: 709, 1960).

As far as Dr. Bruns' question about sperm activity is concerned, this was found accidentally. We put a drop of the enzyme combination on a sperm specimen and found a marked dissolution of the spermatic fluid. Under the microscope there was immediate immobility of the sperm. This work has been pursued further, and we found that the immobility lasts for 24 hours.

From that time we tested each compound separately, and using the same solution in which the enzyme was dissolved, we found that desoxyribonuclease has a marked effect, whereas fibrinolysin has a lesser effect. The combination is thus spermostatic, although I am not willing to say at this point that it is spermicidal.

I did not have time to mention this before, but those who' use the enzyme combination in the treatment of cervicitis and vaginitis in patients who wish to become pregnant should keep in mind that the drug inhibits sperm activity.

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Spontaneous premature rupture of the fetal membranes

A review of 363 cases

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THIS is a report on spontaneous premature rupture of the fetal membranes, prepared by the Department of Obstetrics, Tulane Medical School. It presents and evaluates 363 pregnancies and their associated maternal and fetal complications.

The criteria for their selection was in accordance with the present definition of spontaneous premature rupture of the membranes, which is any rupture of the fetal membranes prior to the onset of labor without regard to the period of gestation.

History

A fleeting glimpse of Greek and Roman obstetrics is enlightening for the educated obstetrician who would understand today's modern obstetrics. As late as the fourteenth century the physicians most quoted and who maintained the dominant influence upon the practice of medicine were Hippocrates, Soranus, Celsus, and Paulus. From this we can see that the ancient principles of medicine had become partially founded and the practices had persisted into so-called modern times.

From the Tulane Obstetrical Unit, Charity Hospital of Louisiana.

Presented at the Twenty-eighth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Kansas City, Missouri, Oct. 6-8, 1960.

*Present address, United States Naval Hospital, Philadelphia 45, Pennsylvania. References found primarily in the *ipsissima* verba of Soranus of Ephesus²² show a knowledge of premature rupture of the fetal membranes similar to that which we hold today. Soranus was a Greek anatomist and physician. He has been referred to as the greatest gynecologist of antiquity and received the nickname of "Methodicorum Princeps." He stated:

In cases of difficult labor, the physician should also question the midwife. [Not whether] it is caused by _____, or dryness, or whatever other causes, one should first promote ease and relaxation. And one should neither have immediate recourse to surgery nor allow the midwife long to dilate the uterus forcibly _____. If, however, the fluid has already drained forth, one should instill some greasy fluid into the vagina by means of a small syringe.

Paul of Regina (625-690),²⁴ the last of the outstanding Greek authors on medicine, was quoted by all the distinguished authors of the Arabian period on almost every page of their manuscripts. They seldom failed to honor him as one of the most outstanding physicians of their Grecian masters. Paul stated:

Difficult labor arises either from the woman who bears the child, or from the child itself, or from the secundines, or from some external circumstances, or from the secundines, either because the membranes cannot be torn prematurely, owing to their thickness: for when the waters are evacuated unseasonably, the foetus gets out with difficulty, from the dryness of the parts. Wherefore, if the difficulty of parturition arises from con-

striction and, as it were, impaction of the foetus, we must first endeavor to produce relaxation by injection frequently of hot sweet-oil with the decoction of fenugreek, or mallows, or linseed, or with eggs as a paregoric. Then we must apply catoplasms to the pubes, abdomen and loins, or linseed or of haried water, or of oil and water; and use hipbaths of a similar nature.

Paul recommended the use of powerful shaking, sternutatories, encouragement, holding breath and bearing down, strong smelling things.

Roesslin,¹² about 1517 to 1526, wrote many articles on obstetrics and its difficulties. He attributed the difficulties of delivery to premature rupture of the membranes in many instances.

Gould and Pyle⁹ reviewed many instances in history of "dry birth" and a few are presented below. Montgomery reported a pregnancy in 1857 in a woman who had a daily discharge of amniotic fluid of about 5 ounces. This daily loss of fluid from the vagina continued for 68 days with the loss of 21 pints of fluid. The woman was delivered of a viable child but it died shortly thereafter.

In 1807 a woman was reported to have been delivered 23 days after rupture of the membranes. In 1875 a case was reported of delivery 90 days after rupture. Gordon and Pyle also referred to a case presented by Griffith where there was premature rupture of the fetal membranes at 6 months' gestation, with the retention of the pregnancy to term. This pregnancy resulted in a live infant. These early authors, however, did not speak or write about the development of sepsis in these pregnancies as often as would be expected.

Clinical material

The case reports in this study were selected from those of patients seen and treated on the Tulane delivery unit of Charity Hospital.

In the 4 year period from July, 1955, to June, 1959, there were 51,214 deliveries. The records for this time noted 1,038 cases of spontaneous premature rupture of the fetal membranes, an incidence of 2 per cent. This

appeared to be low in comparison to reports published. This stimulated a survey of a large number of obstetric charts of patients delivered by the Tulane Service from 1955 to the present. This was further associated with a critical evaluation of all patients admitted to the delivery unit from November, 1959, to June 1, 1960. From these, 363 analyses are presented.

The patients treated represent the lowest socioeconomic class; approximately 90 per cent come from the immediate metropolitan New Orleans area, and 10 per cent may travel from as far as 700 miles away. Approximately 85 to 90 per cent of these patients are Negroes and 10 per cent are Caucasians. The race distribution in this analysis was essentially the same, 89.8 per cent Negro and 10.2 per cent Caucasian. Of these, 71 (18 per cent) women did not attend the prenatal clinics and thereby failed to receive the benefits of prenatal care.

Fifty-one per cent of the women were between 20 and 30 years of age. Fifty-nine per cent of these women had been pregnant four or more times (Table I).

The period of gestation was determined by the consideration of menstrual age and weight of the fetus, the fundal height, and the relationship of these to probable maturity as presented by Eastman,³ Streeter,²³ and Litzenberg.¹⁷

Rupture of the membranes was found to occur as early as the fifteenth week of gestation. There were four cases recorded prior to 20 weeks and 207 from 36 weeks to term (Fig. 1).

Diagnosis

The method used for making a positive diagnosis of ruptured fetal membranes included:

A. A complete history with regard to time of rupture, activity of the patient at that time, the color, odor, and volume of the fluid lost, and whether or not the patient experienced any increased fetal activity or vaginal bleeding. Additional associated questions were employed to determine the presence of possible infection on admission.

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B. A sterile vaginal examination was performed with the patient on the delivery table. In this manner an adequate examination with good visualization could be executed. The positive signs were: *Palpatory:* No fetal membranes felt over the presenting part. *Visual:* Observation of fluid, hair, skin of the presenting part, meconium, or vernix caseosa in the vagina or emerging from the cervical os.

C. The laboratory procedure used was a basic (alkaline) reaction to nitrazine test paper when it was placed directly on the external os, in the absence of any bleeding. It has not been necessary or advantageous from experience to employ the use of Papanicolaou smears, frozen sections, or direct Gram stain smears from the vagina or cervix.

Etiology

The causative factor of premature rupture of membranes must be listed as unknown, in spite of the fact that each patient seen from November, 1959, to June, 1960, was carefully questioned in regard to coitus, trauma (vaginal or abdominal), instrumentation (douche, tampons), and type of physical exertion. True spontaneous rupture existed when no known instigating factors could be found. Also, those patients who had been followed in the prenatal clinic were evaluated as to gross cervical infection. Knox and Hoerner14 feel that "Infection in the female reproductive tract, especially in the cervix, can cause premature rupture of the membranes and induce premature labor."

Continuation of pregnancy

In evaluating the outcome of the pregnancy one must consider two general cate-

Table I. Incidence of premature rupture of membranes

Age (years)	%	Gravidity	%
Up to 20	17	i	17
20-30	51	ii to iii	24
31 plus	32	iv or more	59

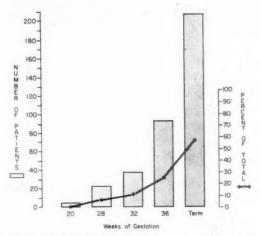


Fig. 1. Incidence of premature rupture of the membranes in relation to weeks of gestation.

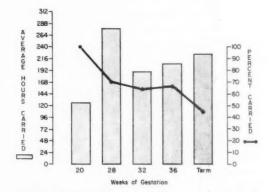


Fig. 2. Continuation of pregnancy in relation to weeks of gestation.

gories: those cases in which the onset of labor and delivery was delayed for a period of time in excess of 24 hours and those cases in which labor and delivery ensued and the uterus was emptied within a period of less than 24 hours. The reasons for delivery in this latter category were either the onset of spontaneous labor and delivery (central rupture at term) or induced labor in the presence of clinical signs of intrauterine infection.

There were 201 patients who carried pregnancies for a period greater than 24 hours; 35 (17.4 per cent) of these developed symptoms and signs of intrauterine infection (Table II).

On closer evaluation 71 per cent of the pregnancies between 20 and 28 weeks' gestation were carried compared to 45 per cent carried for the group of patients 36 weeks to term. One pregnancy was carried 102 days.

Some of the important factors that seemed to affect the survival of pregnancy were thought to be the influence of gestational age at the time of rupture, intrauterine infection, fetal weight, and presentation. Other factors were concerned with the length of time that the membranes were ruptured.

It was found that if the fetal size was small the possibility of termination of the pregnancy was lessened to some extent and mirrored a marked improvement in the prognosis in terms of survival of the pregnancy (Fig. 2).

The survival of the pregnancy was dependent upon the presence or absence of intrauterine infection. This was emphasized by the policy to terminate all pregnancies in which signs of infection developed. This policy has been mandatory from past experiences to prevent overwhelming generalized sepsis so common in this group of patients.

There was a correlation between the actual fetal size and the ability of the patient to carry the pregnancy (Fig. 3). From this total picture in associating fetal weight with prolongation of pregnancy it appeared that those infants weighing between 500 and 1,000 grams were more successfully carried. It was also found that the greater the fetal

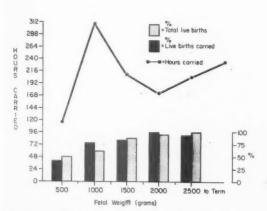


Fig. 3. Hazard of prolongation of pregnancy.

weight, the greater the influence rupture of the membranes had on the development of spontaneous labor and delivery.

Fetal position from our study *did not* show an influence on premature rupture of the fetal membranes (Table III).

Fetal survival

The primary factor in fetal survival was related to maturity. This has been standard in the statistics relating to the survival of infants admitted to the premature infant center who were delivered at Charity Hospital. These factors are compared in Table IV.

Although 50 per cent of the infants weighing 500 grams were admitted to the premature center, none survived. In comparison, in the group of infants weighing 2,001 to 2,100 grams there was a 93.9 per cent survival.

The presentation did have a marked effect on fetal survival. There was a 30 per cent mortality in breech presentations of premature infants, compared to a 7 per cent mortality in the vertex presentation, a rate of 4 to 1 (Table V).

Infection also played a part in relation to fetal survival in the premature and the mature infant (Table VI). There were 28 instances of prematurity associated with intrauterine infection; 6 of these infants died (21 per cent). There were 16 mature births associated with the same complication; one baby died (6 per cent).

We cannot close our eyes to the child when it leaves the delivery room. For even when a live birth results from a pregnancy with intrauterine infection a poor prognosis persists. Edith Potter¹⁶ of Chicago, as well as the Pediatric Department of Tulane University, has found that the vast majority of pneumonias occurring in the premature or mature infant in the first 2 weeks of life had an intrauterine origin.

Thurman,²⁵ of the Department of Pediatrics at Tulane, evaluated all the cases of infants requiring exchange transfusions from July 1, 1957, to June 1, 1960 (Table VII). Here again we see the complications of pre-

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Table II. Continuation of pregnancy

	Ca	Carried		Terminated		
Period of gestation	Infected	Noninfected	Infected	Noninfected	Total	
Prior to 20 weeks	2	2	0	0	. 4	
20-28 weeks	8	9	0	5	22	
28-32 weeks	4	20	1	12	37	
32-36 weeks	10	53	1	29	93	
Over 36 weeks	11	82	6	108	207	
Total	35*	166†	8	154	363	

*Seven stillbirths.

†Ten stillbirths.

maturely ruptured membranes. More than half of the infants requiring exchange transfusion for sepsis and jaundice were born after premature rupture of the membranes.

Sepsis need not be clinically present in the mother to be found later in the infant.

Table III. Continuation of pregnancy in relation to presentation

	No.	Occipito- anterior	Occipito- posterior	Breech
Carried	201	169	23	9
Terminated	162	144	6	12
Total	363	313	29	21

Twelve per cent of mothers in this group showed signs of sepsis with premature rup-

The elapsed time between rupture of the fetal membranes and the development of intrauterine infection shows a definite relationship. Many writers have stated that the longer the pregnancy is carried with ruptured membranes, the higher the incidence of infection. In this study there were 107

pregnancies carried for less than 120 hours with a 12.1 per cent incidence of intrauterine infection compared with 94 pregnancies that were carried for more than 120 hours with an infection rate of 23.4 per cent (Table VIII).

Six hundred thirty-seven Negro infants of less than 2,100 grams at birth with premature rupture of the fetal membranes were evaluated at our institution to determine if the duration of membrane rupture affected the mortality of premature infants (Table IX). From this study 30.18 per cent of premature infants who were delivered in less than 6 hours died. The infants who were delivered after 6 hours or more had an 18.9 per cent death rate. The medical director of the premature infant program felt that this was a significant difference. This will have to be evaluated further for its validity to be proved.

This study showed that 91 (25 per cent) of the patients experienced "spontaneous premature rupture of the membranes" more than once. Eastman³ states that "spontaneous premature rupture" occurs in about 12 per cent of all pregnancies.

Table IV. Infant survival in cases of premature rupture of membranes

	This	study	Premature			Premature center		
Grams	No.	Born alive	Rate (%)	(rate of survival)				
500 and under	6	3	50	0.0				
500-1,000	20	16	60	10.1				
1,001-1,500	30	26	87	55.3				
1,501-2,000	34	32	94	87.0				
2,001-2,100	16	15	94	93.9				
2,101 and over	263	257	98	85.7				

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Table V. Presentation as related to fetal survival

	Breech		Vertex			
	Total	Survived	Died	Total	Survived	Died
Premature Term	24 (75%) 8 (25%)	17 (70%) 8 (100%)	7 (30%) 0 (0%)	149 168	138 (93%) 166 (98.8%)	11 (7%) 2 (1.2%)
Total	32 (8.8%)	25 (78%)	7 (22%)	317	304 (96%)	13 (4%)

Table VI. Intrauterine infection with fetal survival

	Infected			Noninfected		
	Total	Survived	Died	Total	Survived	Died
Premature	28	22	6	145	133	12
Mature	16	15	1	180	179	1
Total	44	37	7	325	312	13

Table VII. Occurrence of sepsis and jaundice

Year	Exchanged (total)	Septic babies needing exchange	Septic babies associated with membrane rupture	Septic babies associated with maternal sepsi
1958	112	36	21 (58%)	3
1959	161	42	28 (67%)	6
1960	144	46	20 (43%)	6
Total	417	124	69 (55.6%)	15

Table VIII. Relationship between time and infection

Time	Infected		Noninfected		Number
	Carried	Stillborn	Carried	Stillborn	carried
To 120 hours or 5 days	13	3	94	7	107
240 hours or 10 days	11	2	30	1	
360 hours or 15 days	7	1	18	0	
480 hours or 20 days	2	0	6	1	94
600 hours or 25 days	0	0	6	0	
720 hours or 30 days	0	0	4	1	
Over 720 hours or 30 days	2	1	8	0	
Total	35	7*	166	10†	201

*Twenty per cent.

†Six per cent.

Complications

Thirteen patients were delivered by cesarean section (3.6 per cent). Three cesarean sections were performed for intrauterine infection after unsuccessful induction. One was for a transverse lie, one for a contraction ring, one for bilateral cystic ovaries creating an extrauterine soft tissue obstruction to the birth canal, 2 for cephalopelvic disproportion, 2 for breech presentation,

and 2 for twins (in one set there was a prolapsed cord with an undilated cervix). One other cesarean section was performed for a partial placenta previa.

Forty-three patients (11.8 per cent) developed intrauterine infection with premature rupture of the fetal membranes. One of these had progressive acute suppurative pelvic thrombophlebitis producing pulmonary emboli, necessitating vena cava ligation.

Management

The management of premature rupture was influenced by: (A) intrauterine infection, (B) presence or absence of labor, (C) gestational maturity, and (D) fetal size.

The presence of intrauterine infection required the immediate emptying of the uterus irrespective of gestational age or fetal size.

The presence of active labor, represented by cervical dilatation and effacement, obviated the course of clinical management to a certain extent. There was no attempt made to interrupt labor by heavy sedation, hormones, or anesthesia; however, all patients were placed on absolute bed rest.

If spontaneous labor did not occur, the gestational age and estimated fetal size were taken into consideration. If the pregnancy was at or near term with an estimated mature fetus, active measures for inducing labor were initiated.

All patients with rupture of the fetal membranes existing for 24 hours or longer were placed on antibiotics. These drugs were continued for a period of 10 days.

Absolute bed rest was continued until there had been no signs of vaginal loss of amniotic fluid for a period of 24 hours. The patients were then ambulated and, if the vagina continued to remain dry, they were discharged with admonitions to go home and to reduce all physical and sexual activity.

Mortality

There were no maternal deaths. Seventeen stillbirths occurred among the 363 pregnancies evaluated.

Comment

Fetal prematurity stands high in the causes of neonatal death, and spontaneous premature rupture of the fetal membranes is the cause of many premature births. If one could gain some insight into the causes and results of prematurely ruptured membranes it would be possible to increase neonatal survival and decrease premature births.

Table IX. Premature rupture of membranes in premature infants

Negro (under 2,100 grams)	6 hours or less	Over 6	Total
Lived	444	193	637
Died	192	45	237
Total	636	238	874
% died	30.18	18.90	27.11

The problems faced with the patients at Charity Hospital are slightly different from those experienced by the average physician. Here one deals with a very low socioeconomic group. The difference will be evidenced in the percentage of complications but the management should not differ in general principle.

No direct etiological factor was discovered. In this study the tensile strength of the membranes was not checked even though there is some evidence that the tensile strength does differ. Danforth² studied this problem and had to come to the conclusion along with Embrey⁶ that spontaneous rupture could not be correlated with the tensile strength of the membranes.

With the increase in age, parity, and repeated injury to the cervix, there would be an increased amount and duration of infection found in the cervice. This may be a definite etiological factor in this reported source, as vaginal and cervical infection was prevalent and in many instances required treatment. This may also explain in part why in this study, once a patient experienced premature rupture, there was a higher incidence of repeating with subsequent pregnancies.

It was shown that survival of the pregnancy and of the infant was influenced by gestational age at the time of rupture. Generally, the closer the pregnancy was to term the greater was the opportunity for the pregnancy to proceed to a satisfactory conclusion for the mother and infant if spontaneous labor did not ensue.

Infection presented one of the major prob-

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lems that had to be reckoned with both for the mother and for the infant. In those pregnancies where fetal maturity was strived for, intrauterine infection developed in 17.4 per cent. These infections were accompanied by a 20 per cent stillbirth rate while in the noninfected gestations there was a 6 per cent stillbirth rate. Where infection was coupled with prematurity the fetal wastage was momentous, being increased threefold.

Infection played a role in prolonging the hospitalization of the mother and necessitated 3 cesarean sections. One mother developed acute suppurative pelvic thrombophlebitis with pulmonary emboli requiring a vena cava ligation.

The presentation of the fetus appeared to influence its survival. There was a 30 per cent fetal mortality sustained in premature breech infants. There was prolapse of the cord in only one pregnancy with prematurely ruptured membranes. This is contrary to the general feeling that prolapse of the umbilical cord is frequent with premature rupture of the fetal membranes.

The complications seen were for the most part general, with the exception of an 11.8 per cent incidence of intrauterine infection. It is an impression (though it has not been proved here), that the prophylactic use of antibiotics had a minimal influence on decreasing intrauterine infection or increasing fetal salvage.

It was felt that the physician should accept the inherent risk to the mother and to the child by endeavoring to obtain better fetal maturity when the membranes rupture prematurely.

The present management consists of bed rest, possible use of prophylactic antibiotics, and intelligent observation with the emptying of the uterus whenever intra-uterine infection presents itself.

Summary

- 1. In this study 363 pregnancies with spontaneous premature rupture of the fetal membranes are presented.
 - 2. No etiological factor was found.
- 3. Factors affecting survival of the pregnancy were gestational age, intrauterine infection, fetal weight, and fetal presentation.
- 4. Infections were present in 11.8 per cent.

Conclusions

It has been shown that spontaneous premature rupture is a cause of premature labor and delivery resulting in fetal loss.

Infection and prematurity played the major role in the production of this wastage. Unfortunately no new methods were found to combat these factors.

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Discussion

Dr. David N. Danforth, Evanston, Illinois. This is a well-documented study of the outcome of pregnancy in a large number of patients with premature rupture of the membranes. The results are generally similar to those which have been reported in other series of cases, and the principles of management have followed accepted and standard obstetric practice.

Certainly it is clear that, of the many unsolved problems in obstetrics, this is one of the most important, since premature rupture of the membranes is one of the outstanding causes of premature delivery; and, of all the causes of neonatal death, prematurity is the most common.

Several years ago Dr. McElin, Dr. States, and I came to what then seemed the inescapable conclusion that some membranes were weaker than others and consequently were unable to withstand the stresses of pregnancy. But when the bursting tensions were tested we found that the clinically weak membranes were at least as strong as those which remained intact throughout labor.

Our conclusion at the time was that all membranes were similar so far as their intrinsic strength was concerned and that those which ruptured early did so because of the secretion of some lytic substance from the endocervix, causing a local dissolution of the membranes in the region of the internal os. Although we have made no further progress with this problem, we are still of the opinion that the cause of premature rupture of the membranes must be sought not in the membranes themselves but rather in the secretions and forces to which they are subjected.

With regard to the clinical aspects of this paper, many important points have been made. Perhaps the most important of these is the incontrovertible fact that when ascending infection occurs both mother and baby are jeopardized. The mother may develop puerperal sepsis and the baby, if it survives, may live to become a cerebral palsy victim.

Most studies dealing with premature rupture

of the membranes have recognized and stressed this hazard of infection. The present authors mention this repeatedly but do not define it or give the means of diagnosis. I think it important that they clarify this point.

In this study, as in others, the use of prophylactic antibiotics is considered to be important. In the case of ascending uterine infection there are 10 (and perhaps more) major groups of organisms which may seriously affect the mother and baby. Unfortunately, there is no single antibiotic which is effective against them all. However broad the spectrum, one or another organism will be unaffected. Only the clarivoyant can select the correct antibiotic for such a case.

To compound the problem, the microbiologists have now described the "replacement phenomenon," a circumstance in which two potentially pathogenic organisms may hold one another in check unless one or the other is destroyed; with the destruction of one, the other becomes pathogenic for the host. It is by this means that the haphazard use of antibiotics for prophylaxis or therapy of undiagnosed fever may "set the stage" for staphylococcal or coliform infections which may be overwhelming and entirely resistant to other antibiotics.

In view of these facts, current thought is clearly against the use of antibiotics for prophylaxis against potential infection. Moreover, the present study shows clearly that in premature rupture of the membranes they are not effective in preventing infection. Hence, on all counts their use in cases of simple, uncomplicated, premature rupture of the membranes should be discarded.

In frankly infected patients with fever and foul vaginal discharge the situation is quite different, for here one faces the hazards of puerperal sepsis and fetal anoxia. Chloramphenicol is probably the least offensive agent in such a case, and it may be used until the direct smear for predominant organisms or the culture and sensitivity tests show some other antibiotic to be preferable.

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Dr. WILLIAM F. MENGERT, Chicago, Illinois. Having been associated for most of my professional life with large maternity services of about the same type as described by Dr. Ekvall, that is, serving underprivileged and mostly Negro patients, I have been much interested in the fact that the incidence of prematurity in such a service will range from 11 to 12 per cent. In private services and in hospitals where the patients are socially and economically privileged, the incidence of premature birth is in the neighborhood of only 3 or 4 per cent. It seems to me, therefore, that economic and social status is a definite etiological factor.

We have all seen instances of partially dilated cervices in late pregnancies, and it would seem obvious that a patient who is not obligated to much physical endeavor and who is able to live without financial stress during the latter part of pregnancy has a much better chance of going to term without rupture of the membranes through a partially dilated cervix than does the relatively underprivileged woman who must perform hard physical labor. Whether or not coitus is a contributary factor, I do not know. It is very difficult to get a history of coitus.

Since we could not do very much to prevent this accident, we turned our attention to the question of infection. For a couple of years we used the standard treatment when the membranes ruptured prematurely. We brought the patient to the hospital, gave her a course of antibiotics, and then sent her home if she was far from term. If she was near term, we induced labor. Still we got into trouble. There were some intrauterine infections, and we were not satisfied with the results. Then we went back to basic principles; in fact, some of the younger men in the department suggested this. I do not think it is possible to sterilize the vagina by any chemical or any antibiotic; in fact, it is known that this organ is dependent for protection upon certain flora with which the patient lives in symbiosis.

So, considering this idea, when a patient came to the outpatient clinic with a history of ruptured membranes we made a diagnosis on the same basis as the New Orleans group has used. Incidentally, I wish to say that suspicion is not adequate and that there must be objective evidence of ruptured membranes.

Having ascertained this, no antibiotic was given. We used this procedure for a year or two. Just from clinical knowledge and experience of each of the groups, we are all thoroughly convinced that the results of the second method of management of these patients is infinitely better than those with the first.

Now we have begun a long-term bacteriologic study. We will study vaginal flora of the woman in her natural habitat, obtaining only one culture at the time she comes to the outpatient clinic, and then we will admit her to the hospital. We have some reason to believe that within 24 hours after hospital admission, regardless of whether or not she receives antibiotics, the vaginal flora will have changed and will have become similar to the flora that exist in that particular hospital and on that particular floor, and a flora with which she is not necessarily living in symbiosis.

Dr. Ekvall (Closing). I would like to answer the question Dr. Danforth asked, as to how the diagnosis of infection is made. We use the three basic criteria which I think are important in any diagnosis-complete history, physical examination, and laboratory procedures.

A complete history is important because we have had several patients come in with temperatures below 97° F. with obvious generalized sepsis. So, I think all three criteria are important. In taking the history, the patient's reaction at home, the duration of rupture, and details of that rupture should be determined.

Physical examination was done in all instances of premature rupture of the membranes, as previously stated. If the discharge found at the time of examination was foul, a direct smear and culture were made to identify the predominant organism. If, as a result of laboratory or physical examination, signs of infection were found, vigorous treatment was given.

The main organisms that we find in culture are the paracolon bacilli and Escherichia coli, which seem to respond best to a penicillinstreptomycin complex. If the patient has marked sepsis, aqueous penicillin in intravenous infusion is given. In less severe cases, a stacked dose of 1.2 million units intramuscularly with 1 Gm. of streptomycin is given. Then the patient receives 600,000 units of aqueous penicillin every 4 hours and 0.5 Gm. of streptomycin every 6 hours. This is continued until we feel an adequate blood level has been obtained.

I hope this clarifies the use of antibiotics. In addition, however, we use antibiotics prophylactically. If a patient's membranes have been ruptured for more than 24 hours it has been the policy on our service to use antibiotics. As many of you who have seen large numbers of patients from this socioeconomic group realize, often fingernails are long and are packed with dirt and feces. In many instances, the soles of the feet are encrusted because these women have not worn shoes. So I think this represents a problem of general, over-all body cleanliness that is not encountered in the average private practice.

A comment or two on Dr. Mengert's remarks: we have found in New Orleans, as a shortage of

beds develops, that we have to put beds in the hall. We can say almost exactly before we start fever rounds at 4 p.m. and 8 p.m. that it will take almost the entire period until the time for the next fever rounds to work-up these patients to determine the etiology of their fever. If we can keep our patient census down to the post-partum and antepartum wards, we find that our problem with intrauterine infection is very much decreased.

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Late irradiation changes in vaginal cytology

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The early effects of radiation therapy upon exfoliated cells of the female genital tract have been frequently reported upon during the past decade.2, 3, 4, 7 Little has been written, however, about the cellular changes that are noted over a prolonged period of time after therapy. In 1947, Ruth Graham³ briefly described changes seen 6 months to 15 years after the completion of radiation therapy for carcinoma of the cervix. Zimmer9 recently reported his observations on a group of 19 patients who had cytologic studies one to 14 years after treatment. He described changes which he believed were associated with previous radiation and which he had found in the majority of the cases that he had studied. The alterations that he considered to be late sequelae of radiation treatment were not evident in the smears taken from 100 postmenopausal women who were used as controls.

In view of the lack of more precise information relative to this problem it was felt that a more detailed investigation of this subject with use of standard and fluorescent staining techniques might be of help in the evaluation of smears taken many years after treatment.

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> Presented at the Twenty-eighth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Kansas City, Missouri, Oct. 6-8, 1960.

Materials and methods

One hundred and thirty-nine smears were obtained from 124 patients and prepared by means of the Papanicolaou staining technique.6 Fifteen of these patients had smears obtained on two separate occasions. One hundred and twenty-seven duplicate smears taken from the same group of patients were studied with the fluorescent staining method described by von Bertalanffy.1 All of the patients had been treated with pelvic irradiation 6 months to 25 years before the smears were obtained, and all were clinically free of disease when the smears were taken. Each patient was evaluated relative to the presence or absence of infection or atrophy of the vagina. Ninety-nine of the patients studied had been treated by standard methods of radium and beam therapy for carcinoma of the cervix. Thirty-two patients had received preoperative radium therapy via intrauterine and vaginal applicators for endometrial carcinoma, and 8 patients had received radiation to the pelvis for the control of benign gynecologic disease. The histories and smears of 8 patients who died of cervical carcinoma were also reviewed. Cytologic studies had been performed on "these patients 6 or more months after completion of radiation therapy. As controls, a group of 20 smears on normal women over 10 years postmenopausal were reviewed.

Results

Review of this material revealed changes in many of the smears which differentiated them from the smears of nonirradiated patients. Each case was classified as showing good, mild, or no late radiation change, dependent upon the extent of these findings. The slides without such changes did not differ in any respect from those of normal postmenopausal women who had not received pelvic irradiation.

The microscopic characteristics of the

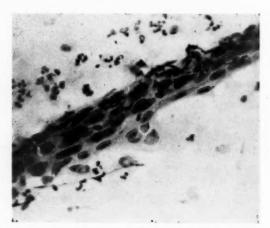


Fig. 1. Cell clump containing cells with indistinct cell borders and large, homogenous, slightly irregular nuclei, some of which are spindle shaped. (Papanicolaou stain. ×300; reduced ½3.)

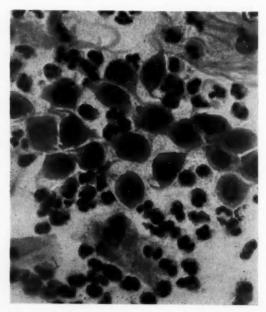


Fig. 2. Benign late radiated cells showing loss of cytoplasmic-nuclear ratio in several of the cells. (Papanicolaou stain. ×500; reduced ½.)

smears showing late radiation change revealed the presence of predominantly basal and parabasal cells with a relatively clean background devoid of many white blood cells. Cell clumping was prominent with the cell borders in these clumps being indistinct and the nuclei being somewhat enlarged and irregular with a homogenous appearance without chromatin clumping (Fig. 1). The cells within the clumps were frequently fusiform in shape and contained spindle-shaped nuclei. In the smears showing more pronounced late radiation change the nuclei were larger, with frequent loss of normal cytoplasmic-nuclear ratio (Fig. 2). Many of the nuclei assumed bizarre shapes and were hyperchromatic with little chromatin clumping noted (Figs. 3A, 3B, and 4). These nuclei on careful study could usually be readily distinguished from the nuclei of tumor cells. Cell swelling, with enlargement of both nucleus and cytoplasmic content, was also prominent. Multinucleated cells were frequently encountered. In many smears a peculiar netlike background of amorphous light pink material was noted (Fig. 5). Some of the nonspecific findings, such as cell swelling, loss of cytoplasmicnuclear ratio, and cell clumping, could not be specifically identified as late radiation change, yet they were present in a considerable number of the smears.

With fluorescence microscopy, using the acridine orange technique, large brightly fluorescent yellow-white to green-white nuclei were seen. The variation in nuclear size was considerable. The cytoplasm fluoresced a dull orange-red which was somewhat deeper than that of normal basal cells but much less than is seen in malignant cells. Cell clumping was common. The presence of these findings was considered indicative of late radiation change; however, at this early stage in our investigations and without further experience we are not prepared to associate these changes positively as being specific late radiation change. Since they were sufficiently suggestive, though, we noted the presence of late radiation change whenever these characteristics were apparent.

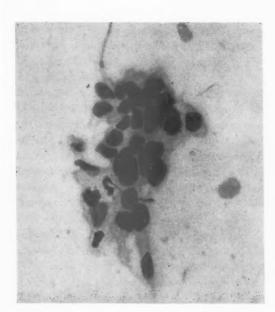


Fig. 3A. Cell clump containing enlarged bizarre shaped hyperchromatic nuclei. (Papanicolaou stain. ×300; reduced 1/9.)

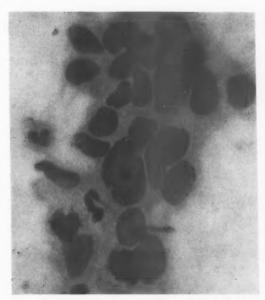


Fig. 3B. Higher power of same group of cells in Fig. 3A. These nuclei are atypical and represent late radiation change within the cells. (Papanicolaou stain. ×500; reduced 1/4.)

With the standard Papanicolaou cytologic technique 36 smears showed good late radiation change. Sixteen of these presented such a severe degree of atypism that only after careful re-evaluation were they withheld from a "suspicious" classification. Sixty smears displayed mild late radiation change and 37 revealed no such change. Six smears were considered unsatisfactory for study. Repeat studies were done on 15 patients 2 to 18 months after the first smear, and the findings in each case on the second examination were consistent with those seen on the first.

The patients varied in age from 30 to 77 years. No relationship could be shown between the age of the patients at the time the smears were taken and the degree of late radiation change.

Correlation of the type of disease treated with the degree of late radiation change revealed that the patients treated for cervical carcinoma showed the greatest degree of cytologic response as well as the severest degree of cellular atypism. Twenty-eight (30 per cent) of these patients showed good

late radiation change and almost half of these displayed a severe degree of cellular atypism (Table I).

The length of time after treatment at which the smears were obtained did not influence to any significant extent the relative degree of late radiation change (Table II). Even in the group of patients treated more than 10 years before this study, over half revealed some degree of response.

Twenty-four smears revealed a netlike background described by Zimmer⁹ as one of the findings characteristic of late radiation effect.

With the fluorescence microscopy technique 103 smears displayed findings consistent with late radiation change and 24 showed no evidence of such change. In comparing the results of the fluorescent and Papanicolaou techniques, agreement was noted in 92 cases and disagreement in 29 cases. In 22 cases the routine Papanicolaou smear showed no radiation change and the fluorescent staining technique did, whereas in 7 cases the Papanicolaou method revealed the presence of radiation change and fluo-

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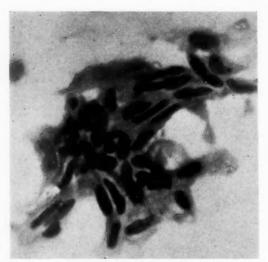


Fig. 4. Hyperchromatic "fiber" cells. Nuclei appear homogenous without chromatin clumping. These must be differed from the fiber cell shed in the presence of invasive carcinoma. (Papanicolaou stain. ×500; reduced ½.)

rescence microscopy did not. Fifteen of the 16 patients showing severe cellular atypism with standard cytologic techniques did not reveal fluorescence consistent with malignant cells in the smears. A smear for fluorescent screening was not obtained on the other patient.

The histories and clinical courses of 8 patients who had died of cervical carcinoma and from whom smears had been taken more than 6 months after completion of treatment were reviewed. All of these patients had frozen pelves and metastatic disease, and one had metastatic carcinoma in the vagina. Smears were available for review on 4 of these patients and all were negative for tumor cells and showed good to fair estrogen effect. The smears were not available for restudy on the 4 other patients; however, the reports all revealed no evidence of cellular atypism.

Comment

The use of vaginal cytology as a means of detecting recurrence or persistence of malignant disease in postirradiated genital malignancies has become an accepted procedure. Hall,⁵ in a study of 99 treated cases

of carcinoma of the cervix, reported on 5 patients who developed positive smears long before clinical evidence of recurrence of carcinoma. He felt that cytology was a valuable adjunct in determining the status of the patient adequately treated and that the patient with a positive smear for malignant cells should be considered to have a recurrence, no matter what the clinical findings until all efforts had been expended to confirm the presence of tumor. Also of interest in his report were the 2 patients with questionable malignant cells who had no evidence of recurrent carcinoma and the 7 with negative smears who had or developed persistent or recurrent carcinoma.

It is our impression that the "late radiation smear" can be confusing and misleading and that great care must be taken in differentiating the atypical changes frequently seen from tumor cells. Sixteen of the patients studied with the Papanicolaou technique had smears which were originally thought to be suggestive or strongly suggestive of malignancy. A careful review of the slides revealed the changes present to differ from those seen in the presence of carcinoma. In one of these patients the changes noted 5 years

Table I. Relationship of disease treated with degree of late radiation change

	Deg	Severe atypism		
Disease treated	Good	Mild	None	in smear
Cervical carcinoma Endometrial car-	28	41	24	13
cinoma	6	16	10	2
Benign gynecologic disease	2	3	3	1

Table II. Relationship between length of time after treatment and degree of late radiation change

Years after	Deg	Severe atypism		
treatment	Good	Mild	None	in smear
6 months to 5 years	24	41.	23	11
5 to 10 years	9	12	8	4
10 or more years	3	7	7	1

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after treatment were so striking as to warrant the smear's being classified as strongly suggestive of malignancy (Fig. 6). patient had been treated with radium and external irradiation in 1950 at the age of 46 for late Stage II carcinoma of the cervix. At the time the suspicious smear was obtained the patient clinically showed no evidence of recurrent neoplasm; however, a radical hysterectomy was performed in January, 1956. Detailed examination of the specimen revealed only the presence of atypical epithelial hyperplasia (dysplasia) of the cervical epithelium which was believed probably related to radiation effect (Fig. 7). At the present time the patient is well and clinically free of cancer. In reviewing the smear the cytologic findings appear to be compatible with dysplasia and not with invasive carcinoma. It is our feeling that such cases should be carefully evaluated, and, if warranted, a fractional curettage and multiple biopsies of the cervix done. Further therapy should be deferred unless tissue sections or clinical evidence strongly suggests the presence of tumor. Recurrent carcinoma of the cervix is usually not found within the cervix itself but is most commonly found as extension through the parametrium and retroperitoneal pelvic areas. Such recurrent tumor will not shed tumor cells into the vagina where they can be picked up for vaginal cytologic study. This certainly is emphasized by the 8 cases in which the patients, all of whom had negative vaginal smears, died of recurrent or persistent carcinoma. The presence of cellular atypism resulting from prior radiation may be seen coincidentally in the presence of deep pelvic tumor. This may account for some cases similar to those reported by Hall,5 where clinical evidence of recurrent carcinoma develops long after a "positive" smear.

From the clinician's standpoint, when a smear obtained on a previously irradiated patient is reported as suspicious or positive for malignancy, the smear should be carefully reviewed, with the changes that can be produced as a result of the prior treatment taken into consideration. The nuclear

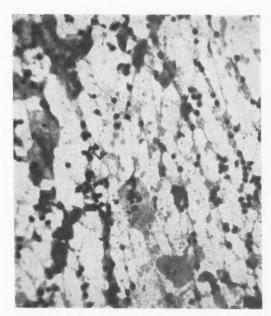


Fig. 5. Netlike appearance of smear background frequently seen in smears years after radiation. (Papanicolaou stain. ×250; reduced 1/4.)

atypism resulting from irradiation differs from that seen in malignant cells. Although hyperchromatism is frequently present in late radiated cells, chromatin clumping is not prominent and the nuclei have a homogenous appearance. Most of the cellular atypism is seen in cells arranged in clumps. Multinucleation and cellular swelling are also not uncommon features. Another factor not consistent with the presence of cervical cancer⁷ is the absence of precornified and cornified cells in these smears. In contrast to this was the finding of fairly good estrogen effect in the 4 smears reviewed on patients who died of cervical carcinoma. Wachtel⁸ has even suggested using the cornification index as an aid in detecting the presence of recurrent cervical carcinoma-a high index in postmenopausal women suggesting the presence of neoplasm. The use of fluorescence microscopy in making the differentiation between the cellular atypism resulting from prior radiation and the atypism seen in the presence of malignancy may be an additional aid. However, it is our feeling that careful study of the usual cytologic preparations by means of the Papanicolaou stain will suffice.

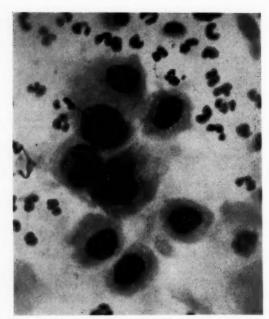


Fig. 6. Severe atypism noted in vaginal smear 5 years after radiation treatment for cervical carcinoma. (Papanicolaou stain. ×500; reduced 1/6.)

Summary

1. One hundred and thirty-nine smears obtained with use of the Papanicolaou technique from postirradiated patients 6 months to 25 years after therapy were reviewed.

- 2. Findings were noted consistent with protracted effects of radiation in 72 per cent of the cases studied; these were classified as showing good or mild late radiation change. These changes were seen as long as 25 years after therapy.
- 3. Twenty-six per cent of the smears displayed good late radiation change, of which 44 per cent showed severe cellular atypism. All of the patients were clinically free of recurrent or persistent tumor.
- 4. One hundred and twenty-seven duplicate smears studied by means of the fluorescent staining technique were also reviewed. Findings were noted which were suggestive of, though not considered to be specific for, late radiation change. Significant differences in interpretation between smears studied by means of this technique and the Papanicolaou technique were apparent.
- 5. The knowledge of prior pelvic irradiation must be taken into consideration when vaginal smears are evaluated, and when severe cellular atypism is noted this must be differentiated from that seen with carcinoma.
- 6. Clinical evaluation is still the most important factor in determining the presence of recurrent or persistent pelvic carcinoma.

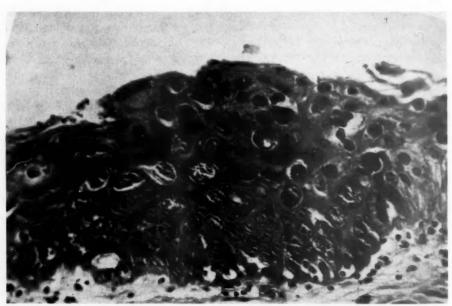


Fig. 7. Section from cervix on patient with smear seen in Fig. 7, showing severe atypical hyperplasia believed related to late radiation change. (Hematoxylin and eosin. ×250.)

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Discussion

Dr. F. J. Hofmeister, Milwaukee, Wisconsin. Dr. Edward Birge, pathologist at Milwaukee Hospital, and I have been interested in the problems of interpretation of Papanicolaou smears of previously irradiated patients. It is essential that cytologist and clinician join efforts to prognosticate the effects of irradiation therapy.

Our experience has been similar to that of others: (1) cancer cells present immediately following therapy are not significant; (2) cancer cells existing 6 to 8 months after therapy indicate the necessity for further investigation and possibly for additional therapeutic measures; (3) cells with malignant characteristics found after a year or more following therapy create many problems. These cellular patterns, when not accurately interpreted, result at times in faulty evaluation by the clinician. Errors in clinical judgment result in unnecessary intervention and, at times, major complications instead of cure. Not all patients will be fortunate enough to have the excellent result as reported by the essayists when atypism resulted in radical operation and microscopy revealed dysplasia. Major surgery added to full irradiation therapy is a major cause of massive tissue destruction and multiple fistulas.

Dr. Birge reviewed our slides and has confirmed the presence of the types of irradiation changes described by the essayists. These changes, however, were not present in the smears of all our postirradiation cases. The majority of the mears of irradiated patients, especially those which could be classified as showing late irradiation changes, presented only the changes of atrophy. Occasionally, the cells present seem to show a follicular effect, and it is questioned if exogenous estrogens had created this picture. This estrogen effect is consistent with the findings of the essayists. It must be remembered that the functioning adrenal gland can be a source of estrogen and that personal response or resistance to irradiation dosage can be such that gonadal

function can recur with resultant ovulation and even-though, of course, very rarely-with recorded pregnancy.

postirradiation therapy Papanicolaou smears accumulated since 1949, a total of 89 patients in whom invasive carcinoma of the cervix was treated by irradiation, were reviewed. Fifteen had no follow-up record; 74 were available for evaluation. Twelve of these 74 have had abnormal smears after irradiation. In 4 of these 12 with abnormal smears, tissue biopsy confirmed the presence of viable carcinoma. Six of the 12 patients with abnormal smears had subsequent negative tissue studies. These smears have been re-evaluated in the light of the criteria set forth by the essayists, and it is the opinion of Dr. Birge that the atypisms thought to be an indication of carcinomatous changes were actually the result of irradiation. Two additional patients on record in the laboratory files had abnormal smears but no subsequent tissue studies. These two sets of smears were also re-evaluated and were considered to show irradiation rather than neoplastic changes.

In addition to the cases listed above, 2 cases of recurrent carcinoma of the cervix, 10 to 15 years after treatment, were diagnosed with the aid of smears when these patients presented themselves to staff physicians with recurrent symptoms.

Evaluation of the cases with positive Papanicolaou postirradiation smears, where biopsy confirmed the presence of carcinoma, seemed to have occurred in those cases where diagnosis could also have been made by clinical evaluation. The patient treated by irradiation or operation for carcinoma of the cervix must be followed by vaginal smears in spite of the fact that distant metastasis and extension may occur without vaginal cytologic changes.

The recent meeting of the Inter-Society Cytology Council on Sept. 23, 1960, has directed attention toward two important reports. Koss and Melamid of Memorial Hospital, New York, reported 7 instances of in situ cancer of the cervix in patients with apparent cures several years postirradiation therapy. Cytology and tissue studies revealed the in situ lesion which the author felt was the manner in which recurrent carcinoma of the cervix begins.

Ruth Graham indicated at the same meeting that she has been able to detect 78 per cent of recurrent carcinoma of the cervix by cytology. In a forthcoming publication she will describe a dark staining small cell not malignant in appearance which she feels is characteristic in cases of recurrence even without evident lesion.

It is apparent, therefore, that in instances where positive postirradiation Papanicolaou smears exist attention must be directed to the fact that biopsy and tissue study must be undertaken. Only biopsy can establish the diagnosis of viable cancer tissue. The statements of the essayists that biopsy is mandatory and that proof of viable cancer tissue or clinical evidence of extension must exist before further definitive therapeutic measures are undertaken must be emphasized.

Cytology, the infant aid in gynecologic diagnosis is coming of age. Use it and its modifications such as fluorescent microscopy wisely and it will become an increasingly valuable adjunct not only in detecting early carcinoma, enabling early

accurate therapy, but in directing additional methods of therapy and in evaluating ultimate results of therapy, both irradiation and surgery.

DR. WALL (Closing). We have found that there is no better way of determining persistence or recurrence of cancer than by clinical assessment. We were unable to detect any differences in the value of the Papanicolaou and fluorescent staining techniques. They both yield a number of cases with atypical cells that make it necessary to assess the situation clinically.

It is not just semantics when we differentiate between recurrence and persistent cancer. Recurrent cancer, in our terminology, refers to cancer that has developed 5 years or more after the original therapy. Persistent cancer probably represents a failure in treatment for one reason or another up to 5 years' time. Unless we keep these facts in mind in assessing the place of these various methods, we will have difficulties in interpretation.

We can easily become panic-stricken by the presence of atypical cells in the cytologist's report. A great deal of harm can be done not only in the diagnostic measures instituted but also in the therapy. It is paramount to depend primarily on clinical judgment as to whether there is persistent or recurrent disease, and the diagnostic measures should not be more complicated than the problem presented.

Repeat cesarean section

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The tremendous advancement in diagnosis and therapeutics which medicine has made in the past century has been accompanied by an even greater progress in preventive medicine. As part of this development, when the use of cesarean section became more common, our fathers coined a phrase, "once a cesarean section always a cesarean section." This dictum and this policy were then followed as part of the program of preventive medicine. Before the antibiotics, the availability of large amounts of blood, the expansion of the resident training program, and the development of the low cervical technique for cesarean section this was no doubt good preventive medicine.

The question now arises, "Is it still good?"
Do we prevent more maternal deaths, fetal deaths, maternal suffering, and exposure of patients to transfusions, antibiotics, and other agents with statistical hazards by following this axiom? Because of emotional factors arising from one's personal experiences the answer indicated by factual information is often difficult to accept.

In order to provide additional factual information several studies of repeat cesarean section have been performed recently. Some are briefly summarized in Table I.

A similar study has been made by the authors in Indianapolis, a city in which al-

most all patients with previous cesarean sections are delivered by repeat section.

Material and methods

The material was collected by reviewing the charts of patients who had repeat cesarean sections during the years 1954 to 1958, inclusive, in each of the 6 hospitals in metropolitan Indianapolis. The operative notes were carefully read so that all cases of dehiscence or incomplete rupture of the uterus would be noted. The cases of complete rupture of the uterus are included even though technically they are not cesarean sections.

The number of deliveries, the total cesarean section rate, and the number of repeat sections are shown in Table II. Approximately one half of the total cesarean sections were repeat sections and about one third of these were accompanied by sterilization.

The obstetricians who either performed or supervised all but 27 of the operations in this study, are almost all either Board-qualified or Board-certified (Table III). Four of the 6 hospitals have residency training programs. It is felt that the complications listed later must be looked upon as inherent in the procedure itself and that they do not reflect incompetence on the part of the operators.

The anesthesia was given by trained physician-anesthetists in 1,358 cases and trained nurse-anesthetists in 104 cases. The type of anesthesia was general in 1,074 cases, spinal in 348, local in 5 cases, and a combination of 2 of the above in 35 cases.

From the St. Vincent's Hospital.

Presented at the Twenty-eighth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Kansas City, Missouri, Oct. 6-8, 1960.

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Table I. Prematurity and mortality in repeat cesarean sections*

	Repeat cesarean sections	Perinatal mortality (%)	Corrected neonatal mortality (%)	Elective premature births	Elective premature deaths	Maternal deaths
Bryant ¹	1,019		0.4	47	2	4
Diddle ²	940	6.5	2.9	40	18	_
Schwartz ³	580	3.1	1.7	27	3	1
Wolff ⁴	200	2.5	2.0	27	0	0
Johnston ⁵	641	2.5	0.8	17	2	1
Baldwin ⁶	616	2.6	1.6	6	2	2
Muller	1,462	3.6	1.5	67	4	1

*Corrected by eliminating stillbirths and deaths due to erythroblastosis and congenital anomalies.

Table II. Repeat cesarean sections in Indianapolis

	No. of live	Sections		No. of repeat	No.	
pital		No.	(%)	sections	lized	
1	12,655	286	2.3	144	1	
2	5,888	173	2.3	92	41	
3	15,938	261	1.6	71	0	
4	13,566	255	1.8	114	35	
5	13,415	780	5.8	439	140	
6	30,280	1,120	3.6	602	289	
Total	91,742	2,875	3.1	1,462	506	

Table III. Personnel performing the repeat sections

Type of operator	
Obstetrician	1,199
General surgeon	27
Resident (obstetrics and gynecology)	236
Type of anesthesiologist	
Physician-anesthetist	1,358
Nurse-anesthetist	104

Table IV. Indications for primary cesarean section

Indication	No. of patients
Cephalopelvic disproportion	484
Prolonged labor	280
Placenta previa	193
Premature separation of placenta	106
Malpresentation	133
Toxemia of pregnancy	116
Diabetes mellitus	30
Prolapsed cord	13
Fetal distress	49
Miscellaneous	103
Unknown	48

Findings

The indication for the primary section was cephalopelvic disproportion in the greatest number of cases, 484 (Table IV). Only one third of the indications were of a recurrent nature. Cephalopelvic disproportion and diabetes were the indications considered recurrent.

Three hundred forty-nine of the patients had been delivered vaginally before the first section (Table V). This figure, of course, becomes significant only if one decides to deliver the patient vaginally after a previous section. Table VI shows the number of previous cesarean sections. The types of primary section and of the present repeat section are shown in Table VII. The large number of classical sections is partially explained by the fact that 142 of the 287 had an associated sterilization.

The maternal complications are listed in Table VIII. Ileus occurred in 28 cases. It was not listed unless Levine or Miller-Abbott suction was utilized. There were 11 recorded cases of thrombophlebitis, but no cases of embolus.

The one maternal death occurred following spinal anesthesia. Cardiac arrest occurred during the procedure, and in spite of temporary success with cardiac massage the patient died the next day.

Another patient required 8 pints of blood with emergency hysterectomy. She was hospitalized 23 days, developed hydronephrosis, and later returned to the hospital for 21 days with severe homologous serum jaundice

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but survived. Another who developed an abscess and a small bowel fistula, later required a bowel resection.

Blood was given to 563 patients. One received 8 units, one 9 units, and one 10 units of blood. A total of 806 units were given (Fig. 1).

There were 53 perinatal deaths. (Table IX). This figure may be corrected, by eliminating stillbirths and deaths due to erythroblastosis and major congenital anomaly, to 22 or 1.5 per cent. The corrected perinatal mortality for premature infants is 9.8 per cent. The corrected perinatal mortality for mature infants is 0.6 per cent.

Four of the corrected premature deaths followed elective section performed supposedly at or near term. These 4 deaths were due to errors in judgment regarding the length of gestation. As Fig. 2 shows, there were 67 such errors resulting in the delivery of premature infants.

The literature indicates this to be a very common error. It has been suggested that the solution is to await the onset of labor in all patients. This, however, in many cases defeats the purpose of repeat section, i.e., the prevention of rupture of the uterus.

The 13 cases of rupture of the uterus in this series are shown in Table X. As in all other reports the complete ruptures occurred more frequently in the classical and the incomplete in the low cervical scar. There was no ileus and no fetal or maternal deaths in this small group.

There were a few cases of vaginal delivery following cesarean section during this period of time but most were unplanned. There were no ruptured uteri, no maternal deaths, and no neonatal deaths associated with these vaginal deliveries.

All of the above-mentioned undesirable occurrences which accompany repeat cesarean section must now be balanced against that one serious, "catastrophic" event which we all fear—rupture of the uterus. In the absence of the primary or other obstetric indication no one would think of repeat cesarean section if we had an absolute guarantee that the cesarean scar would not rupture. This

Table V. Parity at time of primary cesarean section

Parity	No. of patie	ents
0	1,113	
1	195	
2	76	
3	37	
3 4 5	14	
5	13 > 34	9
6	5	
7	5 4 3	
8	3	
9	1	
10	1	

Table VI. Number of previous cesarean sections

No. of previous sections	No. of patients
1	941
. 2	415
3	77
4	23
5	3
6	2
7	1

Table VII. Types of present and earlier cesarean sections

Type of section	Primary	Present repeat
Classical	254	287
Longitudinal low cervical	71	137
Transverse low cervical	540	1,026
Extraperitoneal	8	3
Cesarean hysterectomy	_	9
Unknown	589	0

Table VIII: Maternal complications

	49.
Nature of complication	No. of patients
Ileus (suction required)	28
Wound infections	47
Genitourinary infection	169
Thrombophlebitis	11
Pneumonia	29
Miscellaneous	73
Maternal mortality	1
Antibiotics	522
Days in hospital (average)	7.98
Puerperal morbidity	245

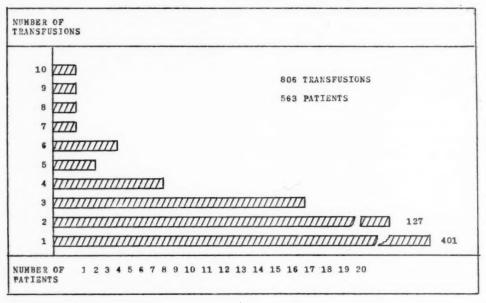


Fig. 1. Transfusions.

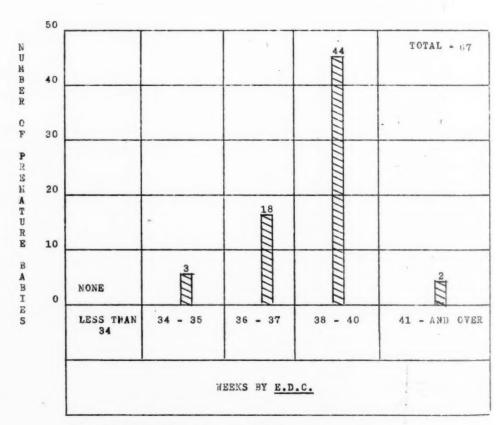


Fig. 2. Premature infants delivered by elective cesarean section.

	Premature			Mature			
	Elective	Not elective	Total	Elective	Not elective	Total	Total
Perinatal mortality	8	22		13	10		53 3.6%
Stillborn	1	4		2	4		11
Neonatal congenital abnormality	2	6		5	2		15
Neonatal erythroblastosis	1	2		1	1		5
Corrected perinatal mortality	4	10	14 (9.8%)	5	3	8 (0.6%)	22 (1.5%

guarantee, as any review of the literature will show, we do not have. The uterine scar does rupture.

Therefore, in order to make a decision it is necessary for us to have a thorough knowledge of this clinical entity. It is of such infrequent occurrence that our only method of study is a composite review of recent literature. There the subject has been covered from two different approaches:

- 1. Reports by those who permit vaginal delivery in selected cases and must of necessity report all ruptured uteri following previous cesarean section.
- 2. Reports by those who study generically the entity of ruptured uteri and therefore in addition to the above include spontaneous and traumatic ruptures in patients who have never had a cesarean section.

For the past 30 years several well-run, well-organized clinics in various localities have had the policy of carefully evaluating each previously sectioned patient and delivering a large percentage through the vaginal canal. In doing this they take very definite precautions to prevent serious sequelae in case of a rupture of the scar. In most clinics these include:

- 1. Thorough investigation of the history of the previous section or sections and the postoperative course.
- 2. Evaluation of the fetopelvic relationship near term by x-ray pelvimetry.
- 3. Availability of cross-matched, typespecific blood during labor.
- 4. Immediate availability of an operating room prepared for cesarean section.

5. Immediate availability of personnel qualified to perform the various functions requisite for that procedure.

Some of these institutions have reported their results, and these are summarized in Table XI. It is necessary to include all cases of rupture of the scar occurring in these clinics, although many of the patients were planned for repeat cesarean section and the rupture occurred before the scheduled operation or the rupture was found at the time of repeat section. Others were found at routine examination of the uterus after vaginal delivery and were completely asymptomatic and benign. As is shown, only 35 per cent of the ruptures after previous cesarean section were of the complete type.

In a more detailed examination of the 33 reported cases of complete uterine rupture we find that the classical scar was responsible for 30 of them (Table XII).

The fetal mortality after complete rupture

Table X. Complications with ruptured uteri

	Incomplete		Complete		
	Classi- cal	Low cervi- cal	Classi-	Low cervi- cal	Total
Number	4	7	2	0	13
Patients					
transfused	3	2	2*	0	7
Ileus	0	0	0	0	0
Maternal					
mortality	0	0	0	0	0
Fetal mortality	0	0	0	0	0

^{*}One patient had 3 transfusions.

Table XI. Vaginal delivery after cesarean section rupture of the uterus

Report	Previous cesarean section	Vaginal deliveries	Total ruptures	Incomplete	Complete
Schmitz ⁷	-	106	6	3	3
Wilson ⁸	943	365	15	6	. 9
Hindman ⁹	-	177	8	0	8
Cosgrove ¹⁰	581	221	12	7	5
Riva ¹¹	142	100	0	0	0
Lane ¹²	697	114	19	16	3
Poidevin ¹³	133	83	0	0	0
Baker ¹⁴	100	74	1	1	0
Lawrence ¹⁵	449	121	2	2	0
Douglas ¹⁶	981	339	27	22	5*
Lawler ¹⁷	179	70 -	4	4	0
Total	4.205	1,770	94	61 (65%)	33 (35%

*Three "window type" ruptures not included.

Table XII. Ruptured uteri (complete) and type of previous section

	Vaginal deliveries	Ruptured uteri complete	classical	Previous low cervical complete
Schmitz	106	3	3	0
Wilson	365	9	9	0
Hindman	177	8	7	1
Cosgrove	221	5	5	0
Riva	100	0	0	0
Lane	114	3	3	0
Poidevin	83	0	0	0
Baker	74	0	0	0
Lawrence	121	1	0	0
Douglas	339	5	3	2
Lawler	70	0	0	0
Total	1.770	33	30	3

Table XIII. Fetal mortality in complete rupture of the uterus

	No. of		Fetal mortality			
Report	vaginal deliveries	Rupture	Classical	Low cervical		
Schmitz	106	3	2	0		
Wilson	365	9	7	0		
Hindman	177	8	6	1		
Cosgrove	221	5	4	0		
Riva	100	0	0	0		
Lane	114	3	3	0		
Poidevin	83	0	0	0		
Baker	74	0	0	0		
Lawrence	121	0	0	0		
Douglas	339	5	2	0		
Lawler	70	0	0	0		
Total	1,770	33	24	1		

of the uterus is shown in Table XIII. Twenty-four infant deaths occurred after complete rupture of the classical scar. The one fetal death after complete rupture of a low cervical scar occurred in a case where the uterus contained both a classical and a transverse low cervical scar. The time of complete rupture of the scar is shown in Table XIV. Nineteen ruptures occurred before the thirty-ninth week or before the onset of labor and therefore could not have been prevented by pursuing a policy of automatic repeat cesarean section at 39 weeks.

Now let us return to the second type of report in the literature, the generic report of "ruptured uteri" (Table XV). Unless one is specifically interested in this subject it is not probable that he would realize the tremendous difference in seriousness of the spontaneous and traumatic types as contrasted to the postcesarean scar rupture. Both pathologically and clinically they are strikingly different entities. Consideration of the difference in vascularity of a fresh area of torn tissue and the fibrous tissues of an old scar emphasizes the pathologic difference. The statistics shown here further establish the clinical difference. The maternal mortality figures of 20 to 70 per cent which we have imprinted in our minds come from reports of spontaneous and traumatic ruptures of the uterus and not from reports of rupture of the previous cesarean section scar. The

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maternal mortality after rupture of the previous cesarean section scar is indeed minimal.

Summary

The recent literature with regard to repeat cesarean section has been reviewed. A report of 1,462 cases is submitted and analyzed with respect to maternal complications, fetal mortality, and ruptured uteri. Blood was administered in over one third of the cases and 28 patients had ileus requiring suction. There was one maternal death and several severe maternal complications.

The corrected perinatal mortality in the premature infants was 9.8 per cent. There were 67 elective premature cesarean sections with a corrected loss of 4 infants. During the same period, there were 11 incompletely

Table XIV. Time of complete uterine rupture

	Total	Before thirty-ninth week	In labor of after thirty-ninth week
Schmitz	3	2	1
Wilson	9	* 7	2
Hindman	8	4	4
Cosgrove	5	2	3
Riva	0	0	0
Lane	3	2	1
Poidevin	0	0	0
Baker	0	0	0
Lawrence	0	0	- 0
Douglas	5	2	3
Lawler	0	0	0
Total	33	19	14

ruptured uteri and 2 completely ruptured uteri. The latter both followed previous classical sections.

The literature describing the experience of those who have followed the policy of conducting vaginal delivery in pregnancy after cesarean section is reviewed. It is noted that there were no maternal deaths in this group. The literature covering the generic entity "rupture of the uterus" is likewise reviewed. The high maternal mortality rates usually associated with the term "ruptured uterus" occur in the spontaneous and traumatic ruptures of the uterus and not in rupture of the postcesarean scar.

Conclusions

1. The perinatal mortality figures indicate that cesarean section is more hazardous for the premature infant but not necessarily more hazardous for the mature infant.

2. As in all similar studies the number of elective premature deliveries in the reported group was high. This error seems to be quite universal and persistent despite obstetric advances.

3. Rupture of the transverse low cervical scar is seldom complete and therefore seldom hazardous to mother or infant. The same cannot be said of rupture of the classical scar.

4. Rupture of the post-cesarean section scar is not the "catastrophic" event that one finds reported in conjunction with spontaneous or traumatic rupture of the uterus.

Table XV. Maternal mortality reported in studies of uterine rupture

	Spontaneous—traumatic		· Previous section			
	No.	Maternal mortality	%	No.		Maternal mortality
Ware ¹⁸	24	10	41.6	16	0	
Meredith ¹⁹	14	4	28.5	22	0	
Ferguson ²⁰	24	4	16.6	60	1	(?type)
Pedowitz ²¹	53	12	22.6	34	1	(classical)
Burkons ²²	30	6	20	35	1	(longitudinal low cervical)
Ingram ²³	12	5	38.3	1	0	,
Bak ²⁴	37	8	22.2	15	0	
Garnet ²⁵	15	11	73.5	6	1	(classical)
Voogd ²⁶	- 10	1	10	2	0	,
Donnelly ²⁷	26	11	42	13	0	

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Discussion

Dr. Douglas M. Haynes, Louisville, Kentucky. Periodically, the problem of route of subsequent delivery following cesarean section comes up for reappraisal. On such occasions, obstetricians lose no time in aligning themselves on one side or the other as to whether or not the dictum "once a cesarean section always a cesarean section" should be followed. Since data can readily be selected to make a plausible case for either viewpoint, and since each physician takes his stand on that firmest of rocks, his personal training and experience, feeling can run high, and champions of either opinion find themselves spitting into a high wind as far as the opposition is concerned. Drs. Muller, Heiser, and Graham have presented a bewildering barrage of statistics which, so they tell us, have led them to favor vaginal rather than repeat abdominal delivery in "selected" patients; somewhat backhandedly, they base their conclusion on an analysis of repeat cesarean sections in their own city where such operations are frequently performed. Their "controls" are "selected" from the published reports of authors who favor the opposite policy. As one of the latter, I would like to emphasize two points which recur in discussions of this problem, including this morning's provocative presentation.

The first question to be answered is, how great is the danger of uterine rupture through the cesarean section scar? The over-all incidence of

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such rupture which can be culled from published reports is of the order of 2 per cent, but reduction to less than 0.5 per cent is claimed when the previous incision was made in the lower uterine segment. This latter figure is in line with Dr. Muller's report of 11 Indianapolis ruptures in 2,875 operations (0.3 per cent). Of the uteri which rupture many do not, indeed, fall into the category of "catastrophic" accidents: the chance of this seems to be 1 in 100 cases of rupture or less, and death of the patient would result in only one tenth or less of these ruptures. Nevertheless, ruptures of the uterus do occur through previous uterine scars, even though rarely; and some of them are catastrophic, though many are not. Those of us who frequently perform elective repeat cesarean operations are familiar with the sight of the bluish fetal membranes bulging menacingly through a paper-thin defect at the site of the old uterine scar. Admittedly, most such "occult ruptures" might not ever cause trouble if vaginal delivery were elected. Some, however, might, and I know of no method of picking out those few from the others. Of course, this finding does not deter the vaginal accoucheurs, since they do not see it. The answer to the first question seems, then, to depend on whether one wishes to take a small chance of a catastrophe, or a small chance of the usually subcatastrophic complications of cesarean section. To Dr. Muller's statement that "repeat

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cesarean section is not an innocuous procedure," I would reply that neither is subsequent vaginal delivery. Further, the incidence of rupture and its hazards may be only 1 per cent statistically, but it would be a 100 per cent rupture in the woman in whom it occurred.

The second crucial question hinges on the selection of the appropriate patients for postcesarean vaginal delivery. Dr. Muller has enumerated the prerequisites for such selection and has described the ideal setup for the management of such patients. The requirements of this setup are rigorous, and they are obviously designed to safeguard the patient from the consequences of possible catastrophic uterine rupture. Dr. Muller and his co-workers have not suggested that these requirements be modified or eliminated, so I infer that they still consider rupture a potential hazard. If one is to carry through such precautions as insuring immediate availability of an operating room set up for cesarean section and requiring the physical presence throughout labor of responsible personnel qualified to deal with a ruptured uterus, perhaps another vital tissue, the myocardium of the attending obstetrician "sweating out" the labor, ought to be given some share of the total consideration.

I rather doubt that this morning's deliberations will have settled this controversy; but I would like to commend Dr. Muller and his colleagues for their serious exposition of their thesis and their obvious desire to find the solution which is best for the patient with a scar in the uterus. My own failure to share their attitude is an honest difference of opinion on a still open question.

DR. WILLIAM F. MENGERT, Chicago, Illinois. I tried a long time ago to compile masses of statistics on vaginal delivery versus cesarean section after previous section, and I concluded that results are equivocal. I would be almost willing to state that if you have 200 patients with histories of previous cesarean section for "incidental reasons and if you use vaginal delivery in half and abdominal delivery in half, one method would yield just as many living babies and living mothers as the other.

The most important indication for cesarean section is never expressed in a textbook. This is the "avoidance of myocardial scars," because it is so much easier physically, emotionally, and in every other way to perform a section than it is to sweat it out during the long hours in the delivery room.

I think we must realize that the objective of the obstetrician in private practice, particularly if he is dealing with a group in whom the number of children per family is not great, should not be to perform cesarean sections repeatedly because it is easier for him.

Conversely, suppose we have a 17-year-old girl who has had a cesarean section for an "incidental" reason. She has a normal pelvis, and is ready for delivery. It would seem to me only common sense to try vaginal delivery and remove this burden from her.

Therefore, I believe very strongly that individual circumstances should be the deciding factors for this procedure.

DR. FREDERICK J. HOFMEISTER, Milwaukee, Wisconsin. Frequently the further the obstetrician becomes removed from the active conduct of obstetric cases and the more he aligns himself with gynecology, the more frequently he asks the question, "Are there not too many repeat cesarean sections being done?"

The hazard of cesarean section begins with the decision to perform the primary section, thereafter there is a distinct and persistent hazard.

In the service of the Maternal Mortality Committee of Wisconsin, it has come to my attention that in one year there were 36 maternal deaths, 15 with associated hemorrhage, and, of these, half were from rupture of the uterus after previous cesarean sections.

Spontaneous rupture of the uterus is associated with a deficiency of the uterus itself and with labor, which in this present day and age can be combated by intelligent intrauterine palpation. inspection of the cervix, and prompt therapy. However, each year as we consider the maternal mortality statistics of the State our attention is directed to the patient awaiting repeat cesarean section who during the night has spontaneous rupture and either the physician is not notified or the patient does not notify the nurse on the floor or the rupture is such a sudden catastrophe that nothing can be done.

The problem, therefore, is to choose the first section wisely, and to follow through intelligently with the second section, to evaluate the femoral epiphyses by x-ray to determine whether or not the fetus is mature, and to intervene early enough after maturity has been established to avoid this unsuspected, sudden, traumatic rupture of the uterus.

DR. WILLIAM W. JACK, Grand Rapids, Michigan. The material I would like to discuss is taken from an internal medical audit done during 1958 in 28 hospitals—large and small, with and without teaching programs—in 11 different states. This information was gathered by the Commission on Professional and Hospital Activities. The focus of the audit was the fate of the baby as influenced by timing of the operation and the anesthetic.

There were 1,380 cesarean sections in the series and these were divided almost evenly between primary and repeat procedures. In about 72 per cent of the repeat group, "previous cesarean section" was the only recorded diagnosis.

Forty of these babies were born weighing less than $5\frac{1}{2}$ pounds and, of these, 5 failed to survive. The physicians of the individual hospitals who had reviewed these charts, however, seemed to hold the view that if the baby survived, the operation was timed properly. I question this attitude.

The multiplicity of anesthetic agents made analysis difficult but some interesting statistics emerged. Cyclopropane was associated with the highest fetal loss; this was particularly true when this agent was given for longer than 10 minutes before the birth of the baby.

Nine instances of rupture of a previous scar were reported, an incidence of 1:77. There were no maternal deaths in this group with uterine rupture, and 6 of the babies survived.

DR. ARTHUR B. HUNT, Rochester, Minnesota. I do not think the physician's coronary arteries should be considered in this matter. We hear about this more and more. If the physician hasn't enough courage to practice obstetrics, then he should enter the practice of radiology or dermatology. I think the only question is what is best for the patient. Conversely, there is no virtue in doing something the hard way just to be doing it the hard way.

I believe as Dr. Mengert does—that each case ought to be evaluated carefully on the basis of individual feasibility of vaginal delivery.

DR. MULLER (Closing). I fully realized this was a controversial subject before we ever brought it up for discussion. I make no attempt to settle it. I think one thing we can agree on is that there are a lot of emotional problems involved.

Regarding the discussion, I would like to challenge the view that with repeat cesarean sections we have only minor catastrophic events. I think the physicians who were involved in the cases that had 10, 9, and 8 blood transfusions with repeat cesarean sections would classify these complications as very catastrophic events.

I believe that we have all chosen a difficult specialty. With our problems, we should not choose the easy solution, but should choose the difficult one if that solution seems to be the better way.

Postoperative morbidity from cesarean section

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E. STEWART TAYLOR, M.D.

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CESAREAN section has become a substitute for vaginal delivery in the solution of many complications of pregnancy and delivery. This trend has been established both as the result of the high fetal and maternal morbidity associated with major operative obstetrics performed vaginally and as a result of the increasing safety of cesarean section. Recognizing this trend, and being a part of it, we have been impressed that patients experiencing cesarean section often have a postoperative course that may be described in terms varying from uncomfortable to harrowing. While death as a complication of cesarean section is rare, the postoperative course of a cesarean section patient is more fraught with complications than that of patients undergoing other intra-abdominal operations of similar magnitude.

One might describe the ideal, and perhaps the desired, postoperative course following cesarean section. This would be a postoperative course characterized by a mild rise in temperature during the first postoperative day, mild discomfort about the lower abdomen for 3 to 5 days, freedom from sepsis, hemorrhage, distension, and embolus, and, finally, hospital discharge on the sixth or seventh postoperative day. Such a benign postoperative period is not the usual course of events after cesarean section. Some pa-

tients become severely ill either as a result of the operation or as a result of the operation and the obstetrical complication for which it was used.

We have analyzed 200 consecutive cesarean sections in regard to postoperative morbidity. There have been two objectives: (1) to tabulate the amount of morbidity, and (2) to discover factors that have contributed to postoperative morbidity.

Materials

The charts of 200 consecutive cesarean sections performed at Colorado General Hospital and Saint Joseph's Hospital between February, 1959, and December, 1959, have been the subject of the study. The operations were performed by residents and attending staff of the two institutions. The cesarean operations were performed for a variety of indications, which may be grouped as shown in Table I.

We have considered febrile postoperative morbidity to be a temperature elevation to 38.0° C. (100.4° F.) occurring on any 2 of the first 10 days post partum, exclusive of the first day.

Other complications which were classified as morbidity were: hemorrhage, wound dehiscence, ileus requiring a Levine or Miller-Abbott tube, thrombophlebitis, vesicovaginal fistula, abscess, pyelitis, endometritis, peritonitis, and respiratory complications.

The complications suffered by patients were assessed in relation to the presence or absence of labor or complications of pregnancy.

From the Department of Obstetrics and Gynecology, University of Colorado Medical Center.

Presented at the Twenty-eighth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Kansas City, Missouri, Oct. 6-8, 1960.

Results

The elective group of 141 cesarean sections had the complications shown in Table II. The listed complication is the major complication, and there is no duplicate listing. In other words, if a patient had a wound separation and a febrile postoperative course, only wound separation is listed.

Thirty per cent of the 141 elective cesarean section patients had a complicated postoperative course according to our criteria.

When cesarean section was used for the solution of abnormal labor or was an emergency, 59 cesarean section patients had the complications given in Table III (one major complication, only, listed for each patient).

Seventy per cent of the cesarean section patients who were operated on for the solution of pathologic labor or complications of pregnancy, such as hemorrhage, had complications in the postoperative course of rather marked degree.

Elective uncomplicated cesarean sections, patients

Table I

not in labor	
Elective repeat	85
Diabetes	5
Rh sensitized	4
Placenta previa	13
Primiparous breech	4
Previous Shirodkar operation	9
Toxemia	2 5
Transverse lie	5
Cephalopelvic disproportion	4
Stillbirth	1
Fetal distress	4
Previous myomectomy	3
Previous anterior and posterior repair	1
Elderly primipara	1
Total	141
Nonelective cesarean sections, patients in bleeding	labor o
Cephalopelvic disproportion	20
Uterine inertia	11
Placenta previa	12
Abruptio placentae	4
Compound presentation	1
Prolonged labor	4
Toxemia	2
Condylomata accuminata	1
Pheochromocytoma	1
Breech	3
	59

Comment

There has been general recognition that the elective cesarean section performed on a patient free of obstetric complications or general disease is a much safer procedure than abdominal section required or used in treatment of complications of labor or pregnancy. A much more difficult postoperative course may be expected when there has been labor, hemorrhage, malpresentation, rupture of membranes, and other complications that lead to cesarean section.

The maternal morbidity associated with cesarean section has been reduced to a minimum by the surgical contributions of Porro¹ in 1876, Sanger² in 1882, Krönig,³ Latzko,⁴ Waters,⁵ and Norton.⁶ The bacteriological and histological contributions by Williams² in 1917, Walthard⁵ in 1919, and Harris and Brown⁶ in 1927 helped to establish concepts in regard to the limits of safety for cesarean section operations after actual or potential bacteriological contamination. By avoiding cesarean sections on infected patients the risk of septic complications was much reduced.

Starting in 1937, with the classic work of Colebrook¹⁰ in London, sulfanilamide was introduced as an effective antistreptococcus drug. This innovation and all the antimicrobic agents that have since been introduced have had a profound effect on surgery and obstetrics.

In spite of advances in surgical technique, bacteriological and pathological knowledge, and the extra security of antibiotics, patients who have a cesarean section today are subject to many serious complications. The complication rate doubles if there has been labor, hemorrhage, or prolonged rupture of membranes. Earlier obstetricians and investigators were faced with high mortality rates. Current practitioners of obstetrics are relieved for the most part of maternal deaths from their cesarean section operations. The febrile morbidity problems and the serious other postoperative problems are still factors to contend with and to be concerned about. Daily¹¹ analyzed 1,000 consecutive cesarean sections in 1939 and found 438 patients, or

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43.8 per cent, had postoperative morbidity. Of the 1,000 patients, 33.4 per cent were in labor at the time of operation and in this group the morbidity rate was 51 per cent. Six hundred sixty-six patients were not in labor and the morbidity rate in this group was 40 per cent.

Complications and morbidity following elective cesarean section are eight times more common than after spontaneous normal delivery in our clinic in spite of the advances in surgery over the past decades. When cesarean section is used as a method of treatment for dystocia and hemorrhage the complication rate is twenty times greater in the puerperium when compared to spontaneous delivery in our institution. When compared to elective hysterectomy performed on women of comparable age the percentages of morbidity from cesarean section is two times higher. 12

It is impossible to review each postoperative patient with complications and define the exact cause of the morbidity. When faced with marked blood loss in patients with placenta previa or abruptio placentae, for example, the obstetrician is forced to operate under undesirable conditions and has to accept the consequences of a prolonged, complicated convalescence.

In reviewing the complications, however, certain omissions in preoperative and postoperative care and operative technique were evident as contributions to morbidity.

Omissions in preoperative preparation of the patient

In some instances a patient was operated on in spite of a full stomach. The stomach should be emptied by either gastric tube or induced emesis by apomorphine before a cesarean section is performed if the patient has taken foods or fluids within a 12 hour period before operation. This becomes important in patients who have had a previous cesarean section and go into spontaneous labor after eating. Patients who have gone into labor before cesarean section or who have had peritoneal soilage at operation should often be maintained on gastric suction for 2 or 3

Table II

Febrile morbidity, only	28
Ileus	13
Atelectasis	1
Vesicovaginal fistula	1
Thrombophlebitis	2
Wound separation	2
Endometritis	4
Pelvic hematoma	1
Intestinal obstruction with bowel resection	1
Pyelitis	1
Total	54

Table III

Febrile morbidity, only	15
Ileus	14
Endometritis	3
Postoperative uterine hemorrhage	3
Pulmonary embolus	1
Wound dehiscence	1
Pelvic abscess	1
Pelvic hematoma	1
Atelectasis	1
Total	40

days after operation, or at least until signs of ileus and peritoneal irritation have diminished. Some patients were fed too early and too much before adequate intestinal peristalsis had returned.

Some patients in whom the membranes were ruptured for a prolonged period or some that were potentially infected because of repeated rectal or vaginal examinations were not given antibiotics early enough. In some instances replacement of blood lost before or during operation was not adequate, and this appeared to enhance the complications after cesarean section. Prolonged general anesthesia seemed to be a factor in the production of postoperative ileus. Conduction anesthesia would have been a better choice for some patients.

Errors in operative technique

Improper choice of the type of surgical procedure was a factor. For example, the low cervical operation was used for cesarean section for anterior placenta previa by some surgeons. This was accompanied by vast blood loss and postoperative morbidity. Less

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difficulty may have been encountered had a classical incision in the uterine fundus been used. The technically difficult extraperitoneal operation was used occasionally when more speed was desirable. The postoperative complications for the extraperitoneal operation were as high as those where the low cervical or classical operations were employed. The extraperitoneal operations in the series of 200 patients were insufficient for differential analysis. In others, the uterine incision was often not isolated from the general peritoneal cavity by moist packs before the uterus was opened. This permitted peritoneal soilage with uterine contents and blood. In our experience, avoidance of peritoneal contamination by aspiration of amniotic fluid through a small opening in the uterus and packing away the bowel from the site of the incision is desirable and contributes to a more uncomplicated postoperative period. Gentle cleansing of the uterine cavity with a warm saline pack will often remove infected strands of membranes and placenta and reduce postoperative endometritis and hemorrhage.

Hemorrhage from the uterine wall during operation should be progressively controlled by hemostats as the incision is made. This was not done for all patients. The alternate plan was to incise the uterus rapidly and let it bleed until after delivery of the infant. Some patients with marked blood loss or

obvious infection have had retention sutures of wire or silk left in place for several days. This may have prevented wound separation. In some instances the speed of the procedure was directly proportional to the morbidity. Operations which took less than 30 minutes had more postoperative complications than those that consumed 40 to 60 minutes.

Conclusions

- 1. Patients without complications and not in labor had a 30 per cent postoperative morbidity rate from cesarean section while patients with complications had a rate of 70 per cent.
- 2. Cesarean section was accompanied by postoperative morbidity eight to twenty times greater than that from spontaneous vaginal delivery, depending on the condition of the patient at the time of operation.
- 3. Before selecting cesarean section over vaginal delivery one should recognize the potentials for immediate postoperative morbidity.
- 4. Morbidity from cesarean section operations can probably be reduced by improved preoperative preparation of the patients, strict attention to established principles of surgery, and good postoperative management.

We wish to express our thanks to 1Robert Jaffe, M.D., and Robert Stanton, M.D., for their technical assistance.

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Discussion

DR. RICHARD D. BRYANT, Cincinnati Ohio. It is not customary in my community to class as morbidity anything other than febrile morbidity. Dr. Dean does not present an over-all

febrile rate, but rearrangement of his figures yields a minimum 24 per cent febrile morbidity rate in elective cases and 32 per cent in nonelective cases. A more detailed analysis of a somewhat larger series of cases, composed of all the sections performed in Cincinnati in the 10 year period 1950-1959 is shown in Table I. An interesting facet of the problem is shown in Table II.

Table I. Postoperative morbidity

Classification	Mor- bidity rate (%)	No. of
Appendectomy (incidental)	8	193
Elective section	8.4	2,218
Aged 40 or over	10	327
All cases	14	6,265
Placenta previa	17	597
Premature separation of the		
placenta	18	439
Transverse lie	23	243
Prolapsed cord	26	105
Failed vaginal delivery		
attempt	27	60
Aged 17 or less	44	158

Table II. Race and morbidity

	Morbidity			
Type of case	White (%)	Negro (%		
Elective sections	6.5	25		
All sections All sections, private	12	33		
hospitals All sections, charity	12	29		
hospitals	25	34		

An astonishing figure in Dr. Dean's series was the 13 per cent incidence of ileus, which, if I interpret his definition correctly, denotes intestinal distention or atony severe enough to make the use of a Levine or Miller-Abbott tube seem advisable. Such a measure was required in only a fraction of 1 per cent in our hospitals.

Concerning definitions, it seems unusual to me to classify sections done on patients with diabetes, placenta previa, or toxemia as elective uncomplicated cesarean sections, especially when the same diagnostic terms are used for nonelective sections. Also, it is not my impression that malpresentation alone contributes to morbidity.

It seems to me a bit unfair to cesarean section to compare morbidity and complication rates following section with the rates following spontaneous normal delivery. More significant figures would be revealed by comparing the rates fol-

lowing section with rates following the vaginal delivery in a similar number of similar cases. It would be interesting to know what the morbidity rates were following the vaginal delivery of patients with placenta previa, disproportion, and transverse lie. And most of us, including the authors, concede that there are certain cases in which the welfare of the baby is traded for possible postoperative complications. This factor of fetal salvage does not appear in simple morbidity and complication statistics.

The ultimate in postoperative morbidity is, of course, death. None occurred in this series. In Cincinnati there were 24 deaths within a year of cesarean section among 6,265 cases in 10 years. The 13 deaths related in any way to the pregnancy or method of delivery are listed in Table III. It appears to me to be more urgent to focus our major attention on these complications rather than on relatively minor ones.

Well over half of the total morbidity in Dr. Dean's cases was made up of febrile morbidity only. If his experience was similar to ours, the vast majority of these were borderline or minimal. Little attention has been paid to the significance of simple febrile morbidity following section. It may have no significance whatsoever, or it may even be a good sign, such as an indication of superior healing, of rapid resorption of blood, vernix, meconium, and amniotic fluid from the peritoneal cavity without the formation of adhesions, or perhaps some other salubrious occurrence. A comprehensive study of the significance of postsection febrile morbidity might be very revealing.

Little was said of the use of antibiotics either prophylactically or therapeutically. In my community the hospitals fell into two distinct categories—those in which the routine prophylactic use of antibiotics was accompanied by a

Table III. Maternal mortality

Cause of death		No. cases
Ergot reaction		2
Anesthesia		1
Hemorrhage		2
Postoperative uterine atony	1	
Retroperitoneal hematoma	1	
Renal failure		3
Bilateral cortical necrosis		
of kidneys	1	
Following shock	1	
Unexplained	1	
Shock (no findings at necropsy)		1
Embolism (pulmonary)		4

reduced morbidity rate, and those in which there was no significant difference in morbidity rates between patients receiving and not receiving antibiotics prophylactically. Thus, it is possible that febrile morbidity rates could be reduced in one or both of the hospitals in Dr. Dean's study if antibiotics were administered prophylactically to all cesarean section patients. Only an on-the-spot survey could determine this.

Each of us has his refinements and niceties of technique which he believes contribute to the over-all success of operative procedures. Unfortunately, few if any of these have been subjected to unbiased criticial analysis. For instance, I personally am staunchly opposed to cleansing the uterine cavity with a wet pack or packing away the bowel. The endometrium and peritoneum are delicate tissues, and the softest pack or sponge is by comparison a piece of rough sandpaper. I would as soon attempt to remove dust from my eye by wiping the conjunctiva with a handkerchief as I would attempt to cleanse or protect the endometrium or peritoneum with gauze. While the bug-a-boo is hallowed by tradition, there is little in current literature to support the belief that rectal and vaginal examinations contribute significantly to morbidity following section.

Dr. Isadore Dyer, New Orleans, Louisiana. I think it is rather unwise to compare private and clinic patients with identical statistical criteria. If I were to show some of the statistics relating to our private practice, as compared to the Charity Hospital group, there would be vast differences in patient reaction, infection, morbidity, and other features.

I would like to ask what type of preparation was used in regard to the abdomen prior to cesarean section. While we were doing the section-hysterectomy studies some years ago, it suddenly occurred to us that the only patients who had any morbidity at all (at least the group with greatest morbidity) were those in whom vaginal preparations were done prior to section-hysterectomy. Therefore, we have ceased to use that procedure.

We have used spinal anesthesia almost exclusively, or local anesthesia, with great success. The intestines are never disturbed. Instead of using Allis clamps, which usually tear the uterine wall, for many years we have advocated the use of a Pennington clamp—a triangular clamp used in hemorrhoid operations. With use of this

clamp, tissues are not bruised, and its use affords an effective way for closing sinuses and saving blood. There is minimal spillage if one or even two suctions must be used.

We attempt to keep amniotic fluid from spilling into the abdomen, and we give an oxytocic agent as soon as the baby's head is born. With these techniques the patient is rarely given blood. She is given nothing at all by mouth for 24 hours except a sip or two of tap water. This is a rigidly maintained routine. After 24 hours, the catheter in the bladder is removed, the dressings are removed from the wound, and the patient becomes ambulatory. We have found these points most helpful in reducing morbidity.

I would like to add one last point. I have no real conviction about this, but I might give you just a personal impression. Just prior to his death Dr. Dieckmann was in New Orleans, and I asked him, "Is there anything new on cesarean section?" He indicated that he and Edith Potter had tried to determine what the difference was between cesarean section and delivery from below in regard to the incidence of hyaline membrane disease. The only difference they could envisage was the fact that women who were delivered from below, as a rule, were dehydrated. So, he said, "We have begun to dehydrate our cesarean section patients 4 or 5 days prior to operation."

We have followed this for several years in elective cesarean sections. Whether it is pure luck, we don't know, but we have not had one instance of hyaline membrane disease with repeat cesarean section.

Dr. Herman I. Kantor, Dallas, Texas. I wish to make a point that was mentioned by the discussant, one which I think worthy of emphasis. The relationship between postpartum morbidity and blood loss had been established many times; yet, I think we, as a group of obstetricians doing cesarean sections, sometimes overlook the amount of blood loss that results.

About 2 years ago we undertook a small study to measure accurately the amount of blood lost during cesarean section. The minimal figures we had amounted to about 600 c.c. exclusive of the amniotic fluid, and the usual figure was between 700 and 800 c.c. Some patients lost considerably more.

Many of these women come in with a hemoglobin value of 10 to 10.5 Gm., and the loss of

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700 to 800 c.c. of blood during cesarean section is frequently the key factor. In our experience this blood loss is more significant in the prevention of postoperative morbidity than the use of antibiotics.

We have been a little disappointed in results of the routine use of antibiotics in an attempt to reduce the febrile type of postoperative complications. However, since this study we have tried in every way to reduce blood loss to a minimum, and in so doing we think we have been able to ameliorate one of the major contributory factors to postpartum morbidity.

Dr. Dean (Closing). We grouped other complications found in the postoperative patient together with morbidity in an effort to prove or to emphasize that even today cesarean section is not as safe as a haircut.

As far as the use of the Levine and Miller-Abbott tubes is concerned, we found that earlier and more liberal use, even preoperatively, of the Levine or Miller-Abbott tube markedly contributed to the comfortable convalescence of the patient, and perhaps in some of these patients the Miller-Abbott tube was placed before a definite diagnosis of adynamic ileus was made.

As far as the elective and nonelective groups

were concerned, we felt that a patient with a diagnosis of placenta previa, who was not bleeding, who was simply in the hospital because of the diagnosis, whose blood replacement had been adequate, and who had a cesarean section performed in the early morning hours in a non-emergency state was an uncomplicated surgical case.

True enough, the patient had a complication of pregnancy; but the operation per se was uncomplicated, as compared to that of the patient with placenta previa with profuse bleeding, who is rushed to the operating room in the middle of the night, and on whom a rapid cesarean section is performed.

As far as cleansing the uterus with a soft, warm saline sponge is concerned, we have no qualms about cleaning an infected uterus in order to remove infected strands of membrane or placenta, just as we have no qualms about using a sharp steel curette on the endometrium in a patient with postpartum bleeding or abnormal uterine bleeding from other causes.

Concerning Dr. Dyer's comments, various techniques were used to prepare the abdomen. I do not believe that in any case was the vagina prepared before operation. We use Pennington clamps for control of hemorrhage as the uterine incision is made.

Amelioration of the hypertension of toxemia by postpartum curettage

CHARLES A. HUNTER, JR., M.D.
WILLIAM F. HOWARD, M.D.
CHARLES O. McCORMICK, JR., M.D.
Indianapolis, Indiana

CONTROL of the hypertension in toxemia of pregnancy has been attempted by diuretics, sedation, and antihypertensive drug therapy. The amelioration of the hypertensive state in the postpartum period is indicated to try to protect the mother from serious complications of this disease, namely, convulsions and cerebral vascular accidents.

Specific therapy for control of the hypertension of toxemia during pregnancy should be directed toward the elimination of the pressor substance. A pressor substance (hysterotonin) has been demonstrated in the decidua, amniotic fluid, and plasma in these patients. Since the decidua has been found to have the highest concentration of hysterotonin, the removal of this tissue at the time of delivery seemed to be a plausible approach.

Patients with toxemia of pregnancy were curetted immediately following delivery of the placenta. The observation that the blood pressure returned to a normotensive level in a much shorter period of time than in the patients not treated in this manner is the basis of this report.

From the Department of Obstetrics and Gynecology, Indiana University Medical Center and Marion County General Hospital.

Presented at the Twenty-eighth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Kansas City, Missouri, Oct. 6-8, 1960.

Methods and material

This study is based on the blood pressure response following postpartum uterine curettage of 70 patients. According to the American Committee on Maternal Welfare classification of toxemia of pregnancy, 60 patients had pre-eclampsia, 3 had eclampsia, 3 had chronic hypertensive vascular disease without superimposed toxemia, and 4 had superimposed toxemia.

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In 69 patients, the uterine curettage was performed immediately following the delivery of the placenta. One patient, with postpartum eclampsia, was not curetted until 33 hours post partum. This case is presented in more detail below. The uterine curettage was done with a specially made, large, sharp curette* as shown in Fig. 1. With as complete curettage as possible, approximately 8 to 20 grams of decidual tissue are obtained. In the majority of the patients, the blood loss has been minimal and no depression of the hemoglobin has been noted following this procedure. No uterine perforations have occurred. The only morbidity ascribed to the uterine curettage was one case of postpartum endometritis which was promptly controlled by antibiotic therapy.

Following the curettage, all patients were placed on a regular diet without sodium re-

^{*}Available from Hemathermatrol Corp., Indianapolis 4.

striction and neither sedation nor antihypertensive medication was administered.

The blood pressure was recorded before, during, and after delivery at least every hour for the first 12 hours following the curettage and then every 6 hours for the remainder of the hospitalization.

Results

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The response of the blood pressure in a severely pre-eclamptic patient following delivery without curettage is illustrated in Fig. 2. This is representative of the gradual return of the blood pressure in these patients, according to reports by Stander,³ Eastman,⁴ Dieckmann,⁵ and Peckham.⁶

Fig. 3 illustrates the blood pressure recordings following uterine curettage in a patient with severe pre-eclampsia. It will be observed that the return to normotensive levels is much faster than the response noted in similar cases not curetted.

The amelioration of the hypertension in a patient with postpartum eclampsia is shown in Fig. 4. This patient was a 17-yearold gravida i, para 0, who was admitted to the hospital with a blood pressure of 150/100 mm. Hg and a total weight gain of 42 pounds during pregnancy. Labor started spontaneously shortly after admission to the hospital and she was delivered vaginally. Immediately post partum, the patient was given morphine sulfate, 15 mg., and reserpine, 0.25 mg., three times a day. Approximately 23 hours after delivery, the blood pressure was 170/90 mm. Hg and she had the first eclamptic convulsion. In spite of sedation and antihypertensive therapy, the blood pressure remained elevated and a second convulsion occurred 5 hours later. A hird convulsive seizure ensued in 8 hours. One hour after the third convulsion, a postpartum curettage was done under general anesthesia. A large amount of decidua-like material was removed from the uterine cavity. All medications were discontinued following the curettage and the blood pressure dropped to 118/70 mm. Hg within 8 hours. For the remainder of her hospitalization, she remained normotensive.

The results of the blood pressure response in the immediate postpartum period following uterine curettage are shown in Table I. In the majority of patients with mild preeclampsia, the blood pressure returns to normotensive levels within 4 to 12 hours after curettage. The majority of patients with severe pre-eclampsia become normotensive within a period of 24 hours.

Occasionally, a "rebound phenomenon" with slight elevation of the blood pressure is observed on the second or third post-partum day. This secondary elevation is not marked and is transitory in nature, usually less than 6 hours, followed by a return to normal levels for the remainder of the hospital stay.

Comment

The role of true toxemia as the initiating factor in residual hypertension following



Fig. 1. Comparison of a normal-sized uterine curette with the special large curette used for postpartum curettage.

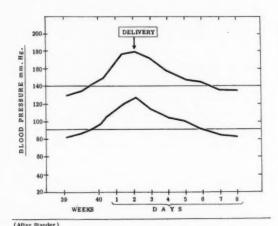


Fig. 2. Blood pressure response of a patient with pre-eclampsia not curetted.

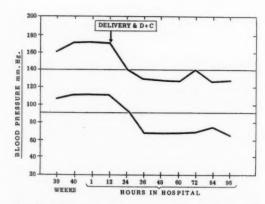


Fig. 3. Blood pressure response of a patient with severe pre-eclampsia following curettage.

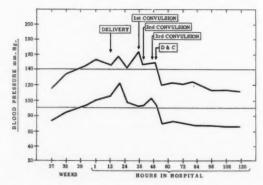


Fig. 4. Blood pressure response of a patient with postpartum eclampsia treated with uterine curettage.

pregnancy is still controversial. However, all observers agree that prolongation of the puerperal hypertension is not beneficial.

The objective of this study was directed toward the amelioration of the hypertension resulting from acute toxemia of pregnancy. No specific therapy was directed toward correction of the albuminuria and edema. Whether or not these two manifestations of toxemia are influenced directly by lowering of the blood pressure is questionable.

In the majority of cases, the onset of postpartum eclampsia is within 48 hours after delivery; therefore, it appears that the time of occurrence of postpartum eclampsia is related directly to the viability of the decidua.

From the results of this study, approximately 87 per cent of the pre-eclamptic patients curetted demonstrated a return of the blood pressure to normotensive levels within 12 to 44 hours. A long-term follow-up study of these patients will be necessary to determine the presence of residual hypertension.

The most dramatic response obtained to date has been the case reported of post-partum eclampsia. This patient failed to respond to antihypertensive and sedative medications. After the removal of the decidual tissue, the patient returned to normotensive levels within 8 hours. Associated with the amelioration of the hypertension, there was also a marked improvement in the patient's sensorium. This marked improvement of the patient, following the curettage, strongly suggests that removal of the decidua was the factor responsible for the patient's improvement.

The 2 antepartum eclamptic patients also demonstrated immediate and persistent returns to normotensive levels. The duration of the prepartum eclamptic process was short in both cases. We can only hypothesize that the response would not be as dramatic in cases of eclampsia of long duration. In these patients, we believe that the persistent hypertension is the result of renal pressor substances which are secondary to pressor substances of decidual origin.

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Table I.	Hours	afte	er cure	ttem	ent	at	which
the blood	pressu	re	returne	d to	pre	pre	egnancy
values							

	Hours after curettement			No re-	
	4	12	24	28	sponse
Pre-eclampsia					
Mild	31	2	1	0	0
Severe	8	3	7	5	3
Eclampsia					
Antepartum	1	0	0	1	0
Postpartum	0	1	0	0	0
Essential hyper-					
tension	0	0	0	0	3
Essential hyper- tension with superimposed					
toxemia	2	1	1	0	0

failed to respond to curettage. This is quite reasonable when one considers that this condition is extrauterine in origin. However, in cases in which the essential hypertension is complicated by superimposed toxemia, the blood pressure will revert to the prepregnancy levels by this procedure.

Failures with this type of therapy are probably the result of: (1) inadequate

uterine curettage, (2) unsuspected essential hypertension, and (3) secondary renal ischemia with activation of the renin pressor mechanism.

The blood pressure response, following uterine curettage of patients with toxemia of pregnancy, substantiates our concepts on the etiology of the hypertension in this disease.

Summary

- 1. Seventy patients with toxemia of pregnancy were subjected to postpartum uterine curettage in an attempt to ameliorate the hypertension.
- 2. In the 67 patients classified as having acute toxemia, 64 exhibited prompt returns of the blood pressure to normotensive levels.
- 3. Three patients with essential hypertension without superimposed toxemia of pregnancy showed no blood pressure response by this procedure.
- 4. The removal of the decidua post partum in patients with acute toxemia substantiates our concepts on the etiological mechanisms involved in hypertension of this disease.

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Discussion

Dr. William E. Copeland, Columbus, Ohio. Dr. Hunter and his associates are to be complimented not only on their excellent work in the identification of hysterotonin, but also for their approach to solving this problem and to proving clinically the rationale of their original concept. The rather prompt amelioration of hypertension in 64 of 67 patients by postpartum curettage is an excellent response to therapy and does substantiate their earlier work.

Certain features of this investigation may not be uniformly accepted and deserve further comment.

- 1. Assuming that in the majority of women with toxemia, ultimate delivery is of prime consideration in treatment of the disease, antepartum or intrapartum therapy may have some beneficial effect that extends over into the postpartum period.
- 2. It is generally felt that prolongation of antepartum toxemia will result in a longer period of residual hypertension post partum, and under these circumstances we would expect the same results or response as noted here.
- 3. The ability of specific drug antagonists to block the action of serotonin has been demon-

strated previously and it has been stated that proteolytic enzymes from the kidney can inactivate polypeptides such as hysterotonin. In toxemia is the kidney incapable of neutralizing hysterotonin, or is it possible that production is so increased that the proteolytic enzymes are incapable of keeping pace?

4. Finally, the minimal complications and morbidity in these 70 patients suggest post-partum curettage as a relatively safe procedure. However, postpartum curettage is still potentially hazardous. Uterine perforation, hemorrhage, and infection will be potential sources of concern and may at times be more hazardous to the patient than the risk of postpartum hypertension treated medically.

It would be of interest to know about the long-range follow-up of these patients regarding resumption of normal menses, the possible development of Asherman's disease, and the subsequent development of permanent vascular or renal changes.

DR. C. O. McCormick, Jr., Indianapolis, Indiana. I would like to elaborate a bit on our technique for curettage. It is a relatively simple operative procedure. We usually use ring forceps and put them on the anterior lip of the cervix, hold them ourselves, or have our assistant hold them. If the assistant does not hold them, we have him hold the uterus.

This procedure can be done in about 5 minutes. I have used both of the curettes presented in Fig. 1, but I prefer the larger one because the procedure can be done more quickly. So far I have been fortunate not to perforate a uterus.

I want to emphasize again that these patients are otherwise treated post partum as normotensive patients are treated. They are put on a regular diet, with no restriction as to salt intake, and they get up as soon as any postpartum patient.

I think postpartum curettage of toxemic patients will decrease the incidence of, if not entirely eradicate, postpartum eclampsia. Just before this study of routinely curetting all toxemic patients, I had 2 patients with postpartum eclampsia. Since performing this operation, I have had no instance of postpartum eclampsia.

As to how long the toxemia has been present before delivery, and what effect that will have on residual hypertension, I will submit the data in Table I. I do not intend to draw final conclusions from this, because the series is too small.

In this total series of toxemic patients, we have had the opportunity of examining 34 of them after they left the hospital. One of these 34 patients was examined for the first time 6 months post partum. This patient had a blood pressure of 160/90. The remainder of these patients were examined at least 6 weeks post partum.

In the group with severe pre-eclampsia, the other case of residual hypertension may not be considered as such. This patient had a blood pressure of 140/84 6 weeks after delivery.

The 2 patients with eclampsia had no residual

Table I. Hypertension following postpartum curettement of toxemic patients

Duration of toxemia (weeks)	Cases	6-8 weeks post partum	Cases	6 months post partum
Mild pre-eclampsia				
1-2	13	0	5	0
3-4	6	0	2	1
5-6	1	0	0	0
7-8	0	0	0	0
Total	20	0	7	1
Severe pre-eclampsia				
1-2	5	1	1	0
3-4	3	0	0	0
5-6	1	0	0	0
7-8	3	0	1	0
Total	12	1	2	. 0
Eclam psia				
1-2	2	0	0	0

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hypertension at the time of their 6 weeks' examination.

Dr. WILLIAM B. STROMME, Minneapolis, Minnesota. I would like to ask simply whether Dr. Hunter and his associates have had any experience with postpartum amenorrhea following such thorough curettage.

Dr. Hunter (Closing). I am one of the first to agree that the duration of the process prior to delivery influences the rapidity with which the blood pressure returns to normal after delivery. It is well documented by many good observations that the duration, rather than the severity, of the hypertension is the significant factor, in that the longer the process persists, the longer it will take before the blood pressure returns to normal. Admittedly, in this series, as you may recall from Table I, many of these patients' hypertension was of relatively short duration.

Concerning the question about the proteolytic enzymes in the kidney and their effects on the circulating polypeptide, be it hysterotonin, angiotensin, or what, it appears that these proteolytic enzymes, which are in the substance of the kidney, are not capable of gaining access to the maternal circulation and inactivating it. This holds true not only in toxemia but also in the unilateral renal disease process in which angiotensin is an incriminating factor. This disease is relatively infrequent.

As far as the question is concerned about postpartum amenorrhea, we have not had any patient who has been classified in this category. To our knowledge, the patients we have followed have all started to menstruate.

The microcosmos and man

THADDEUS L. MONTGOMERY, M.D.

Philadelphia, Pennsylvania

Man's curiosity about himself and his environment seems to be leading him in two opposing directions of research: one, to the exploration of the infinite regions of space; two, to the study of the minutiae of matter. Each of these disciplines has its own instrumentation, its own literature, and its own enthusiastic followers, and the understanding which has grown and the knowledge which seems near at hand defy the limits of imagination.

Actually the two branches of science have much in common. They both require for study instruments of great magnification; and the distances between the constituents of the small and the area in which they vibrate are comparable to the far reaches of space in which heavenly bodies constantly recede. Infinity in the minute constituents of matter therefore is just as real as infinity in astronomical regions.

Fundamentally, size appears no longer to play a significant role in importance, and the smallest unit of structure may be the common denominator of both the atom and the galaxy. The secret of all physical structure probably lies in the constitution of the small and when we have solved that we will also have solved the riddle of the large. In the meantime we probably will have found the answer to the structure of the nucleus, how it responds to health and disease, and how it is affected by old age, bacteria, viruses, and the various protozoan diseases to which the human animal is subject.

No longer are we a few prehistoric humans defying the dinosaurs. Now we are a huge and sprawling population concerned with the minute denizens of the earth. Actually man is a late-comer to this globe. The molecules, the protein complexes, and the unicellular organisms were here millions of years ago, with the "firstest and the mostest." Some of these have reacted in a friendly fashion and helped sustain our existence. Others compete with us for space and food. Finally, there is a group which would destroy us as often and as rapidly as environmental conditions would permit.

It is with the latter group of inimical bodies that my paper is concerned—and actually only with a small segment of this army of the opposition, for time, knowledge, and my own experience will permit no more. I wish to deal specifically with that group of the enemy which we thought we had beaten and sent thoroughly on the retreat, namely, bacteria. This innumerable host has remarshaled his forces and descended upon us with new and confusing attributes.1 He has attacked those nearest and dearest and now we are particularly concerned with how newborn man can survive this bacterial onslaught and can enter upon a safe and reasonably comfortable existence. Perhaps bacteria also in their own peculiar fashion of thinking and planning are endeavoring to determine how they can survive the forces of man and in each of the two camps there is subtle planning of strategy and tactics. Pierre Teilhard de Jardin,2 in his intriguing book The Phenomenon of Man, speculates upon the state in which nuclear material begins to think or at least to act instinctively. As we learn more of bacteria and cell reactivity

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Table I. Types of bacteria cultured in pregnancy (Lang, Fritz, and Menduke)

	Trichomoniasis (%)	Candidiasis (%)	Trichomoniasis and Candidiasis (%)
Lactobacillus	56	73	70
Gram-negative enteric rods	28	24	. 29
Strict anaerobes	5	2	3
Streptococcus faecalis	60	33	62
Hemophilus	2	0	7
Staphylococcus	53	42	43
Others	4	2	4

we wonder whether this stage of thinking has not already been reached in the bacterial world and we may well be disturbed as to what new turn their strategy will take.

As we well know, the battle with bacteria begins early. While the fetus in utero is ordinarily well protected from bacterial life in the outside world, the first and most important zone of defense, the membranes, may disrupt prematurely and expose the products of conception to an invasion of a motley horde of bacteria from the cervix and vagina. Studies performed in our clinic by Lang, Montgomery, Wise, Fritz, Prince, Mandle, and others, 3, 4 of the bacteria of the vagina associated with trichomoniasis and candidiasis in the vulva of patients admitted in pregnancy and in the cervix and vaginal vault of patients with premature rupture of the membranes reveal the wide spectrum of bacteria which may be present under various conditions (Tables I-IV). Some of these are pathogenic to the mother, many of them are pathogenic to the fetus. Slemons⁵ was one of the first to point out the lesions of the membranes, the placenta, and the umbilical cord which are related to premature rupture of the membranes and the progression of infections from the vagina of the mother through the placenta to the

Assuming that infection from the vagina has not occurred, nevertheless it is only a few minutes after birth until the anterior nares of the newborn and umbilicus are colonized with the bacteria of the delivery room and a few hours until the gastrointestinal tract becomes the Elysian field of bac-

Table II. Types of bacteria cultured in trichomoniasis (Lang, Fritz, and Menduke)

	Pregnant (%)	Non- pregnant (%)
Lactobacillus	56	35
Gram-negative enteric rods	28	51
Fecal streptococci	65	40
Staphylococcus	53	16

Table III. Vaginal cultures of mothers on admission (Montgomery, Wise, Fritz, et al.)

	Ward patients		Private patients	
Cultures	44		38	
Coagulase positive	13	(30%)	3	(8%)
Type 44A	3	(6.8%)	1	(2.6%)

Table IV. Culture of cervix in 50 cases of premature rupture of membranes (Prince and Randall)

Diphtheroids		43
Hemophilus		36
Micrococcus		34
Nonhemolytic streptococcus		25
Yeast		25
Microaerophilic streptococcus		18
Lactobacillus		13
Staphylococcus aureus	470	13
Alpha hemolytic streptococcus		11
Escherichia coli		9
No growth		8
Neisseria gonorrhoeae		6
Proteus mirabilis		5
Aerobacter aerogenes		3
Beta hemolytic streptococcus		3
Pneumococcus		2
Beta hemolytic streptococcus (Gr. A)		1
Anaerobic streptococcus	1	(?)

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Table V. Cultures of umbilical cord segments 24 hours after delivery (Bernstine, Ludmir, and Fritz)

Group 1. Coagulase positive staphylococci	33%
Group 2. "Intestinal type"	83%
Escherichia coli	
Aerobacter aerogenes	
Bacillus proteus	
Proteus rettgeri	
Paracolon	
Pseudomonas	
Enterococci Lancefield Group D, etc.	
Group 3. "Respiratory type"	22%
Neisseria catarrhalis	
Neisseria sicca	
Hemophilus	
Diplococcus pneumoniae	
Bacillus streptococcus	
Group 4. Anaerobes	24%
Clostridium	
Bacteroides	
Anerobic micrococci	

Table VI

	R	Rooming- in		Vursery
Nasal cultures of infant	s at a	lischarge		
Cultures	50		49	
Coagulase positive	37	(74%)	46	(94%)
Type 44A	18	(36%)	37	(76%)
Periumbilical cultures of	of infe	ants at d	ischa	arge
Cultures	50		49	
Coagulase positive	23	(46%)	39	(79%)
Type 44A		(26%)		

terial growth. No exposed area of the newborn is free from the attack—the skin, the eyes, the genitals, the breasts, the umbilical cord, or the intestinal tract. Of all of these areas, the most susceptible is the freshly ligated and severed cord, the partially collapsed channels of which lead directly into the blood stream and tissue spaces of the fetal body. Umbilical cord infection is not a disease of the past; it is one of the most common sites of neonatal infection. Hurst, Hardyment and associates, Silber and Ferguson, and Van Gelder and co-workers call attention to this important portal of

entry. Bernstine, Ludmir, and Fritz¹⁰ in our department have cultured segments of the umbilical cord periodically after delivery and have demonstrated the teeming bacterial life which is present in this area (Table V). Montgomery and associates⁴ noted the colonization of the nares and umbilicus with staphylococcus on discharge (Table VI).

It is as if this army of marauders has passed the word along, "Boys, here is a particularly lush and palatable dish—let's go." Actually the attack is just as bold and brash as that, and if the bacteria take hold a human life may be sacrificed at its birth. It is estimated that from 13 to 20 per cent of perinatal mortality is the direct result of bacterial infection. 11-13

It is easy to shift the responsibility for perinatal infection to the pediatrician inasmuch as most of the manifestations of infection take place after delivery. This allocation of responsibility to someone else is neither fair nor any longer permissible. Obstetricians must accept the fact that they have selected and set up the environment in which their patients are delivered and that many of these perinatal infections start before delivery and, therefore, are their responsibility to solve. The environment into which a baby is first introduced after birth, the obstetrician created. The fact that this environment is not always favorable must be confronted. Also, in many hospitals the ob-



Fig. 1. Bags, boxes, and bottles.

d



Fig. 2. Soiled shoes from the locker room.

stetrician shares with the pediatrician the responsibility for the architectural setup and control of nurseries.

Concerning this problem of the newborn and his introduction to a bacterial world several approaches may be considered: (1) separation of the newborn from environmental bacterial life; (2) reduction of environmental bacteria to an insignificant or low level; (3) elimination of pathogenic organisms from early contact with the newborn; (4) modification of the propensities

of bacteria; and (5) elevation of the level of resistance to injurious bacteria or destruction of bacteria at the onset of infection.

Separation of the newborn from environmental bacterial life

Small vertebrates have been raised in a germ-free environment as a special project of the Lobund Institute of the University of Notre Dame over a period of 32 years. The results of their observations; research of the Walter Reed Army Institute of Research, Washington, D. C.; the Department of Pathology, University of Ngaia, Japan; The National Institutes of Health of the United States; and the Institute of Histology of the University of London were reported in a symposium of the Seventh National Congress for Microbiology in Stockholm in 1958.¹⁴

It is evident from these investigations that "life processes in germ-free vertebrates are possibly in many ways different from those in conventional animals, the latter living in close and often changing symbiosis with microbes." It is also evident that small ani-

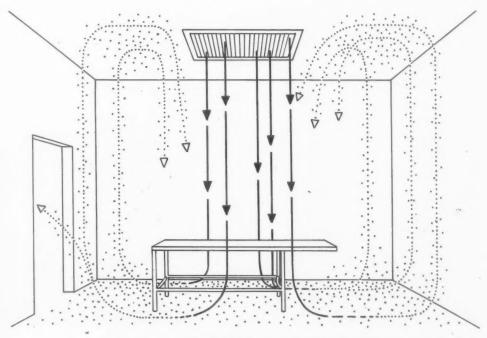


Fig. 3. Effect of air currents in operating room on dust.



Fig. 4. The acoustical ceiling.

mals under these circumstances fare not too badly. Growth is more rapid on the same amount of nutrition. Wounds heal readily with minimal reaction. There is very little tissue reaction to foreign bodies, cancer cells, homologous tissues. Organismal disease of the skin and intestines is unknown. Dental caries does not occur in germ-free rats. However, it is noted that in the absence of the usual intestinal flora the stimulus to gamma-

globulin production is removed and upon return of the animal to its usual environment it becomes extremely susceptible to the pathogenic organisms of the animal house.

These researches demonstrate how difficult it is to exclude bacteria from the environment of a growing organism and the housing required would not prove attractive to the human parturient and his offspring. A bacteria-free life does not seem practical in the near future.

Perhaps these researches parenthetically shed light on the bacteria-free conditions in other planets and star collections and indicate what may happen in these areas when man brings his fellow bacterial travelers from the earth.

Reduction of environmental bacteria to an insignificant or low level

Assuming that numbers play an important part in the mass effect of bacterial invasion, there is more to be said in a practical way for the reduction of the number of environ-



Fig. 5. Packaged goods in cabinets.



Fig. 6. Shoe cleaning at the end of the day.

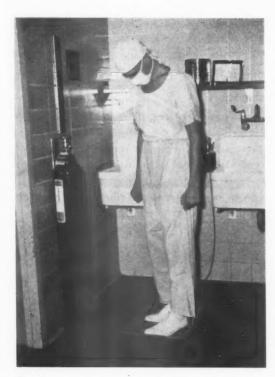


Fig. 7. Preparing to enter delivery room.

mental bacteria in the surroundings of the human newborn than for their elimination. This has to do with simple matters of cleanliness and good housekeeping, disciplines which seem extremely hard to maintain in hospital practice where so many hundreds of individuals are coming and going each day and so few people can be interested in conscientious and thorough elimination of dirt. Hospital journals are replete with articles15-19 on wall and floor cleaning, antiseptic procedures in the laundry, transportation of materials, and all of the infinite minutiae of procedure which would help overcome the nosocomial factors in institutionally acquired infections.

Fortunate indeed is the obstetric service whose delivery room and nursery attendants are "good housekeepers." Training schools for nurses used to start their probationers off with a mop and a scrub bucket; now they begin with psychiatry and biochemistry.

A few years ago as a member of our local committee on hospital-acquired infections,

I started out with a camera to record some of the conditions which seemed to be contributing to our rising rate of infections and what was done to correct them. Boxes, bales, and buckets (Fig. 1) were found on floors where they were rarely moved for cleaning. Suction and oxygen tubing dangled in dirt. Shoes which would not be taken on a camping trip were worn in the delivery rooms (Fig. 2).

While the ventilating system of the new pavilion did not introduce bacteria it kept dust in constant circuit, picking it up from the floor and depositing it on walls, ceilings, patients, newborn babies, and instrument tables (Fig. 3). A special problem in our new pavilion was the rough acoustical plastered ceiling of asbestos and other fibrous material from which stalactites of lint and bacteria dangled and periodically fragmented. These could never be adequately cleaned (Fig. 4) and became a progressively increasing menace to aseptic technique. The fiber composition of hospital dust has been commented upon by Pressly.²⁰

As a result of these visual evidences of faulty structure and practices and also in the face of mounting wound infections and neonatal morbidity, remedial measures were instituted. Racks and pedestals were provided for tubing and buckets and supplies were stored in cabinets (Fig. 5). Facilities for cleaning shoes were set up and antiseptic foot mats placed at strategic areas (Figs. 6 and 7). Ceilings were coated with plastic or

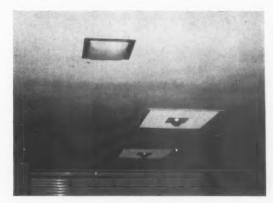


Fig. 8. Smooth plaster ceiling.



Fig. 9. Spraying floor with antiseptic solution.

replaced with smooth plaster (Fig. 8) and floors are regularly sprayed with an iodine solution during operations or deliveries to trap dust and destroy fellow bacterial travelers (Fig. 9).

As a result of this and other improvements in aseptic technique, wound infections have been kept below 1 per cent on the obstetric and gynecologic service and infant morbidity reduced to a minimum. Bacterial studies soon to be published have shown a disappearance of epidemic types of staphylococcus and a marked reduction in the coagulase-positive forms.

With it all, the problems of sanitation and housekeeping in our large institutions are very great. The presence of a full-time sanitary engineer or consulting public health officer would be helpful. I Hospital construction of the future should be such also that as each room is emptied it can be entered by an attendant and hosed down from ceiling to floor and all dust and bacteria washed out through a drain (Fig. 10). Present-day methods of dusting, mopping, and even vacuum cleaning leave much to be desired in regard to elimination of dirt and bacteria.

Elimination of pathogenic organisms from early contact with the newborn

Years ago, before the golden age of antibiotics, when aseptic technique and prompt isolation of infections were standard procedure, a Chicago obstetrician, Joseph B. DeLee, strongly advocated that all maternity patients be delivered either in their homes or in separate maternity hospitals.²² Several

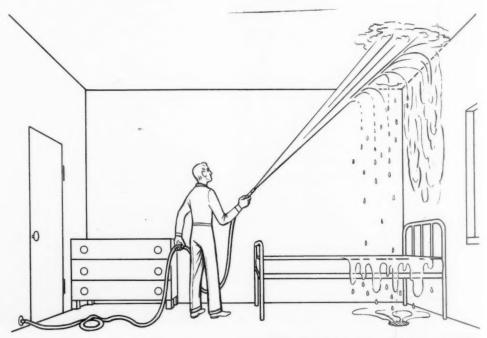


Fig. 10. Hosing down ceilings and walls.

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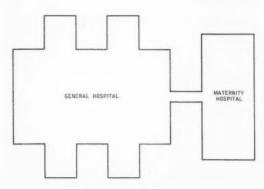


Fig. 11. Relationship of Maternity Hospital to the General Hospital.

such were built about the country but in recent years have been used to house gynecologic or other patients. The sanctity of the maternity hospital has been lost, for pelvic infections and pelvic cancer are certainly not good bedfellows for maternity patients.

We need to return to the principle of the separate obstetric institution, connected only by passages that will make consultation ready and laboratory services available (Fig. 11).

The prompt isolation of infected mothers and babies is accepted as a basic principle in present-day hospital practice and places for these must be set aside and available. In spite of such measures, the central nursery has become and remains the principal problem site for bacterial infection of the entire institution.23-25 Hurst23 has revealed how rapidly new nurseries become colonized. Actually, this is easy to understand, with 20 or 30 little sets of bellows pumping bacterialaden air in and out newborn lungs and one or two harried nurses passing care from baby to baby with too little time for intermediary washing. The larger the nursery population the greater the danger.

The concept of a central nursery area for admission of babies and small peripheral nurseries for subsequent care (Figs. 12 and 13) has improved the situation, but not completely corrected it. Prompt and continued rooming-in of baby with mother is the only measure which provides major protection to the newborn. In 1946 we started this practice in the wards of the Jefferson

and have pointed out its efficacy as a public health measure in subsequent papers.^{26, 27} To this day, we have had no epidemics of infections or even series of related infections of the newborn in the ward service. Recently, we compared the ultimate bacteriology of the newborn in central nursery care and from the rooming-in areas⁴ and some of the findings are listed in Table VI.



Fig. 12. Central nursery.



Fig. 13. Small peripheral nursery.

Hurst²³ raises the question as to whether hospital nurseries may have to be replaced by rooming-in. Over and over again it has been found by epidemiologists that the only way of stopping epidemic infection in the newborn is to take the baby directly from the delivery room to the mother's bedside. If this is good practice in epidemics it is good practice in routine care.

Again if I were constructing new architecture I would have a recovery room for the mothers and a recovery room for babies immediately adjacent to the delivery room (Fig. 14). Each would be kept there for 2 to 6 hours. The mother would then go to her room; the baby would go either to rooming-in at the mother's bedside or to a small nearby peripheral nursery. Both would be discharged in 1 to 3 days if their condition and their home conditions permitted. As I said in a recent paper,³⁹ the hospital is a good place to deliver a baby, but a poor place to board it.

There are, of course, other important considerations in this phase of our topic—nasal carriers of pathogenic organisms and bacterial infections acquired in utero in rup-

tured membranes. Almost everyone around a hospital carries the common hospital flora of bacteria. A few have persistent strains of high pathogenicity. I have been able to reduce these in my own case by intranasal application of neomycin ointment.

As regards the problem of intrauterine infections, much work is going on throughout the world; our own research laboratories of microbiology are actively interested and engaged. Eastman²⁸ was discouraged by the poor results with penicillin but, of course, this antibiotic covered only a narrow spectrum of organisms. Smith²⁹ felt that he had favorable results with streptomycin and oxytetracycline. The tendency today is to get the baby out of the womb when membranes have been ruptured more than 24 hours but there are circumstances where prompt culture of the cervix (Table IV), identification of the predominant organism, and appropriate antibiotic therapy to the mother may improve the environment of the baby.

Years ago, Mayes^{29b} affirmed that injections of merbromin (Mercurochrome) solution in the vagina lessened the morbidity of the parturient patient and her offspring.

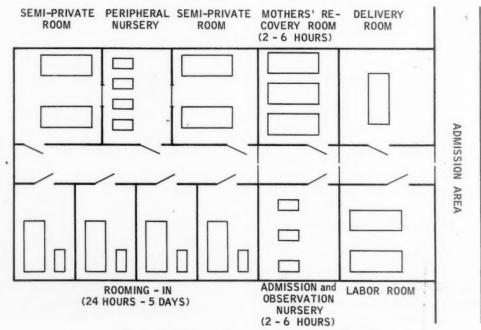


Fig. 14. Diagram of maternity floor accommodations.

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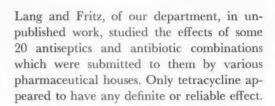
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Fig. 15. Collapsed cord ready for delayed severance.



Modification of the propensities of bacteria

The renaissance which has occurred in microbiology with the discovery of the structure of the cell nucleus and its hereditary elements is doubtless well known. That these elements are subject to mutation and to change in pathogenicity of the organism is now equally well known.¹ If thereby friends can be made of enemies and these friends can protect us from other enemies, a long step will have been taken in our struggle with pathogenic bacteria. This, however, lies in the future.

Of far greater immediate importance is the fact that with proper controls and limitation of the widespread usage of antibiotics, susceptible families of bacteria return and outgrow many of the more formidable groups. Gould³⁰ points this out in an investigation of the effect of environmental penicillin upon the strains of pathogenic staphylococcus.

Perrin Long³¹ states he does not believe that antibiotics should be given to prevent anything. If that statement is kept in mind, the injudicious and free use of antibiotics



Fig. 16. Umbilical cord of 3-day-old infant.

for mild or anticipated infections is curtailed. If infected patients are promptly isolated and effectively treated, perhaps the bacterial flora of our hospitals and communities will return to its previous more innocuous level.

Elevation of the level of resistance to injurious bacteria or destruction of bacteria at the onset of infection

Mudd³² discusses the practicability of enhancing specific resistance to staphylococcal infection by the use of vaccines. Based upon a better understanding of the complex antigenic components of the bacterium, more specific and effective immunizing agents are being utilized in many areas of Europe. Tentative news of some work in this country is reported in one of our news "weeklies." The applicability of such procedures to the field of perinatal morbidity remains to be demonstrated.

The procedures and the antibiotics to be employed in the face of *possible* infection, actual infection, and epidemics of infection of the newborn have received wide comment in the literature. The question of when to administer antibiotics to the newborn infant who has been exposed to prolonged premature rupture of the membranes is under heavy discussion. Kent and Widerman point out the ill effect of chloramphenicol administered to the newborn as prophylaxis against infection.

In spite of the statement of Perrin Long regarding the illogic of administering antibiotics to prevent anything, nevertheless, a smoldering or early infection may kill before the etiological diagnosis can be established.

I cannot leave this phase of the subject without commenting further upon prophylaxis of infection in the umbilical cord and its vessels. Earlier in this paper attention was called to this area as the starting point of some of the most serious infections of the newborn. Boissard and Eton³⁸ add something further in this vein.

In our clinic we are of the opinion that immediate ligation and severance of the cord locks up culture medium in the blood channels which predispose to bacterial invasion. On the other hand, nonligation or late severance and late ligation of the cord permit of complete emptying of vascular channels, collapse of vessels, and more prompt desiccation and resistance to infection (Figs. 15 and 16). In addition, we feel that the umbilicus of the newborn should be dressed as a surgical wound until it is healed.

Summary

The microcosmos, as represented at least by bacterial life, and man share the dubious distinction of communal existence on this earth. The minute forms were here long before the humans; some of them view the advent of the latter in a friendly or at least a tolerant manner; others will have no part of the transgressing and they would destroy human life if given half an opportunity.

The most acute phase of this struggle occurs in and around the circumstances of human birth when young and tender forms unused to such vicious behavior become ready marks for all types of attack.

At one time the human forces thought that they had the battle won and relaxed in their battlements. But the bacteria with amazing sagacity remarshaled their forces, replanned their strategy, and returned to the fray with renewed vigor and remorseless cunning.

One worried corporal in the human army has reviewed the battleground, studied the position of the opposing forces, and called attention to certain modes of attack which he thinks might be useful at the present and worthy of development in the future.

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German measles in pregnancy

HERMAN I. KANTOR, M.D. W. K. STROTHER, M.D. Dallas, Texas

A woman who contracts German measles during a pregnancy usually confronts her obstetrician with a number of difficult and disconcerting questions:

- 1. What are the possibilities that this child will be affected by the disease?
- 2. If the baby is affected, what difficulties will it have? What defects may be anticipated?
- 3. Are these deficiencies permanent or can they be helped?
- 4. Is it proper to perform an abortion in order to prevent the birth of this possibly deficient child?
- 5. Should gamma globulin be used? Does it have beneficial effects in German measles? Will it prevent abnormalities in the child?

The contact of the individual physician with rubella in pregnancy is usually limited. Only the reports from epidemics, if correctly and unemotionally evaluated, should be used as a basis on which these questions may be answered with confidence and equanimity.

The occurrence of an epidemic of German measles in the Dallas–Ft. Worth area in 1958 presented another opportunity to add information toward finding correct answers to these pertinent questions. It was decided to coordinate the experiences of the physicians in the area in order to achieve numbers of statistical value. Attempts were made to avoid the common errors which may be anticipated in such a cooperative study.

From the Baylor University Medical Center.

Presented at the Twenty-eighth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Kansas City, Missouri, Oct. 6-8, 1960.

Background from the literature

Congenital abnormalities in the baby resulting from maternal infection with German measles were described by Gregg⁴ in 1940. As a result of a widespread epidemic in Australia, he was able to carry out a retrospective study of 78 infants. His anticipated incidence of fetal involvement was indeed awesome—80 to 90 per cent abnormal children. Fortunately, this frightful figure has not been borne out in subsequent epidemics.

The report by Blattner¹ lists the incidence of affected babies as 10 to 12 per cent in the first trimester, and "little risk" when the maternal disease occurs in the second or third trimester. He recommends using gamma globulin early, but proof of its value has not been established. Krugman and Ward⁵ also suggested its use. They also advise convalescent phase plasma and convalescent phase gamma globulin.

Greenberg, Pellitteri, and Barton³ report a series of 104 patients with rubella in the first trimester, in which 48 therapeutic abortions were performed and 12 patients aborted spontaneously. An additional 10 were lost to any follow-up. From the remaining 34 patients, 28 normal babies were born, 3 babies were stillborn, and 3 showed congenital defects.

Dekeban, O'Rourke, and Cornman² describe multiple malformations in one baby whose mother had severe rubella in early pregnancy. Among the defects attributed to the ravages of the virus, this infant showed congenital cataracts, congenital heart disease, perception deafness, microcephaly, and mental deficiency. The major alterations is

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fetal embryonic development are ophthalmic, cardiac, or neurological.

In a panel discussion, Mengert⁶ pointed out that a diagnosis by history alone may be fallacious. Abortion, if performed, must be based on a foundation more solid than an unverified maternal history of rash and fever. Many physicians now urge exposing young girls to rubella to avoid these complications of the disease in early pregnancy.

Material for the study

These cases are reported from a questionnaire which was sent to three groups of physicians: (1) the staff of Baylor Hospital, Dallas, Texas, (2) the Dallas-Ft. Worth Obstetric and Gynecologic Society, (3) the Dallas Academy of General Practice.

The criteria for reporting these cases were carefully listed:

- 1. The diagnosis must have been verified by a physician. Telephone and lay diagnoses as well as "possible cases" were excluded.
- 2. The physician was requested to establish, as accurately as possible, the trimester of pregnancy in which the illness occurred. Data sheets for this purpose were supplied.
- 3. The reports were not called in until well after the patient had been delivered to permit evaluation of the baby by the obstetrician or pediatrician.
- 4. A follow-up letter was sent in order to ascertain effects on the baby not evident at the time of birth.

In spite of these attempts at rigid control, several sources of error are acknowledged as possible:

- 1. Some infections with the ECHO viruses are indistinguishable in their clinical features from rubella. Our epidemiologic studies did not include virus cultures. On the other hand, if these diseases are clinically indistinguishable, perhaps it is reasonable to consider them together.
- 2. Dating an incident in pregnancy may often be inexact. We tried to minimize this discrepancy in timing by reporting as trimesters of the pregnancy rather than as weeks of gestation.

3. Our follow-up studies to discover late effects on the babies may be incomplete. Some complications, such as deafness or mental retardation, may have been missed unless they were brought to the attention of the obstetrician. In our report we included all known cases.

Results

The results are presented in Tables I and II.

Table I. Total patients in series and incidence by trimesters

Total patients reported	92
Rubella in first trimester	72
Rubella in other trimesters	20

Table II. Occurrence of congenital defects

First trimester cases		72
A. Abortions		17
Induced	11	
Spontaneous (early)	6	
B. Term deliveries		55
Normal, living, well	47 (85.5%)	
Heart defective	3*	
Eye, cataracts	2	
Stillborn	2†	
Deaf	1‡	
Second and third trimester ca	ises	20

*One additional patient, listed under cataract, had a congenital heart lesion.

†One of these may have resulted from placenta previa rather than rubella.

Determined when the baby was 9 months old.

Comment

On the basis of our experiences in this epidemic, we may suggest, in approximate numbers, the following responses to the questions posed at the beginning of this report:

- 1. When maternal rubella occurs in the first trimester of a pregnancy, there is an 85 per cent chance that, if carried to term, the baby will be normal.
- 2. Of the fetuses that are affected by the virus, 10 per cent will be aborted spontaneously early in the pregnancy. If the pregnancy does continue, 4 per cent of the babies

will be stillborn and 11 per cent will show some abnormalities. These abnormalities may be cardiac, ophthalmic or neurological, singly or in combination.

3. Some of these deficiencies may be amenable to surgical help. The neurological defects are irremediable at this time.

4. The sociologic and religious aspects of inducing an abortion must vary with the individual patient. Many states limit medicolegal criteria to those conditions which threaten the life of the mother. No blanket policy may be established, but these experiences reveal that if the pregnancy did carry to term, induction of an abortion would have destroyed 85 normal children in order to prevent 11 from being born with deficiencies.

5. Since gamma globulin was not extensively used, our experiences were insufficient to answer these questions.

Occasionally, deficiencies which occur in a newborn infant may be *incorrectly* attributed to a maternal viral infection. In one of our normal, pregnant women, we noted a fairly constant fetal heart rate of 40 per minute. Congenital heart block was suspected. In the third trimester, long after this slow heart rate was detected, the patient had severe rubella. The baby was born with the intraventricular septum absent. Such a lesion, if not discovered before the rubella, might have been attributed to the virus.

Summary and conclusions

- 1. This cooperative report includes 92 patients with German measles in pregnancy.
- 2. Seventy-two occurred in the first trimester. Of these, there were 55 term deliveries with 47 normal babies, apparently not affected by the disease.
- 3. Approximately 11 per cent of the living term babies had defects apparently caused by the disease. Approximately 4 per cent were stillborn.
- When German measles appeared in the second or third trimester, all of the babies were normal.

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Discussion

Dr. J. Phil Redgwick, Omaha, Nebraska. I believe there has been some loose thinking on this subject because of the 70 to 90 per cent incidence of abnormal infants reported in the original series out of Australia. As the author brings out, their disease must have been different from ours because the majority of reports from this country show only a 10 to 12 per cent incidence of malformations and then only if the infection occurred during the first trimester. This lower percentage should certainly better our feelings and I hope lower our therapeutic abortion rate. I would question the spontaneous abortion figures and the term stillborn figures of Dr. Kantor unless they are carefully compared with those in a noninfected group.

My figures resulted from questionnaires sent

out to members of the Nebraska State Obstetrical Society. The response from the members was 66 questionnaires returned out of 88 sent. The combined series showed a congenital deformity rate of about 12 per cent. This rate is similar to the author's and the anomalies were also similar in type.

I was amazed at the high percentage of our obstetricians using prophylactic gamma globulin, as we are again in the field of fallacious historics. Did the neighbor to whom she was exposed have German measles? Like the author, I canno evaluate the efficacy of gamma globulin.

DR. ISADORE DYER, New Orleans, Louisiana One of the sources of panic in our area is the pediatricians. If a pregnant patient's child ha 961

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ana th ha measles, the pediatrician will say, "You had better get gamma globulin because you might have a deformed baby." Also any other pregnant woman who has come into contact with the children who ride in the same station wagon to school gets gamma globulin.

There is another fault in our area, I believe, in that some of our very well-known and wellqualified physicians will tell their patients, "You have a 50 per cent chance of having an abnormal

baby. Whatever you want me to do, I will do. If you want to have an abortion, I will arrange it. If you want to carry the baby, then run the risk." That is an improper way to have patients make decisions for you.

I have always felt that if German measles was a reportable disease, and if it were possible to report every case of German measles in pregnancy, the statistics showing congenital defects would be further diluted.

An outline for the organization of perinatal mortality studies

JOHN H. HOLZAEPFEL, M.D. BROOKS RANNEY, M.D. KENNETH S. NICOLAY, M.D. Columbus, Ohio

That brief period of human existence between the twentieth week of fetal life and the end of the first month of postnatal life—the perinatal period—presents a greater hazard to the individual than does any other. It is then that the peak level of human wastage occurs. The magnitude of the problem is illustrated by the fact that the number of deaths of viable fetuses and newborn infants in the United States alone approximates 165,000 annually. Thus, 10 per cent of all deaths occur during this 5 month interval.

An even larger number of potential lives, 425,000, are lost as a result of spontaneous abortion early in pregnancy. When to these figures are added those of permanent physical and mental disabilities which develop consequent to the process of birth, the total casualties related to these problems reach nearly one million every year.

The Central Association of Obstetricians and Gynecologists has taken an active role in the organization of perinatal studies in hospitals within its geographical limits. In 1957 Williams¹ read his paper on "Perinatal Mortality" before this Association. He stressed the need for conjoined staff studies in order

to effect a reduction in deaths and morbidity in the perinatal period. The Maternal Welfare Committee of the Central Association of Obstetricians and Gynecologists was requested to prepare a report on current studies being carried out in its area. Ranney² presented this report in 1959. It showed that 118 of the 242 hospitals responding had a Perinatal Mortality Committee. Thus, there has been a favorable gain of 18 per cent within the last year (Table I).

It is to be hoped that 100 per cent of the hospitals will soon be making an active investigation of perinatal mortality and morbidity.

To determine the make-up of personnel comprising present functioning committees, questionnaires were sent to 282 hospitals; 222 responded—a return of 79 per cent. Table II indicates the committee make-up.

To aid and to encourage the function of such hospital committees the Material Welfare Committee of the Central Association of Obstetricians and Gynecologists has prepared an "Outline for the Organization of Perinatal Mortality and Morbidity Studies." These outlines will be available upon request to this Committee.* We do not wish to pre-

Report by the Maternal Welfare Committee of the Central Association of Obstetricians and Gynecologists.

Presented at the Twenty-eighth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Kansas City, Missouri, Oct. 6-8, 1960.

^{*}Forms are now available from which the different types of institutions may pattern perinatal committees. These forms vary from simple to the more complex IBM code. They are representative of those which might be adapted to different hospitals situations. These may be obtained from Kenneth S. Nicolay, M.D., 4635 Wyandotte, Kansas City, Missouri.

Year	Hospitals	Perinatal committees	%
1959	242	118	48
1960	222	146	66

Table II. Make-up of perinatal committees

Number of hospitals with perinatal committees	146
Obstetric staff participation	145
Pediatric staff participation	120
Pathology staff participation	94
Nursing staff participation	54
Anesthetic staff participation	48

sume that this outline is the final answer for any given hospital. Each institution is its own entity and must solve its own problems. The type of study is dependent upon the size of the hospital and its staff. Following the "Outline" are 3 separate, representative forms for case reporting.

Organization of a committee to study perinatal mortality and morbidity

I. Personnel

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- A. Representatives of all hospital services: includes obstetric, pediatric, pathology, anesthetic, nursing, and administration departments.
- B. Success of the committee is dependent upon preliminary organization and review of noteworthy cases before presentation to the attending staffs.

II. Records

- A. A regular, current record review is essential to the functioning of this committee.
- B. History meetings should be held at no longer intervals than one month; weekly meetings are to be preferred.
- C. Uniformity and completeness of recording are the basis for accurate reporting.
- D. Only selected cases warranting full staff consideration should be presented with the care and detail of a clinicopathologic conference.

E. Data are confidential and available for study to the participating hospital only.

III. Aims of the committee

- A. To make a complete case study of all fetal deaths.
- B. To allow a free exchange of ideas between obstetric, pediatric, pathology, anesthesiology, nursing, and administrative departments.
- C. To maintain objective self-criticism without attention to personalities.
- D. To reappraise medical management, particularly in areas of labor, delivery, and the newborn infant in order to improve care wherever possible.
- E. To educate at all levels: patient, student, house staff, and attending staff.
- F. To evaluate and elicit all facets of cases on a local basis in order to create better care and understanding.
- G. To review morbidity with the same care as mortality in order to correct adverse conditions if at all possible.

IV. Method of reporting

- A. To be effective committee reports should be given at regular, well-publicized meetings.
- B. Reports out of committee should be held at least monthly.
- C. Conference meetings with other staffs should be conducted with anonymous records.
- D. Cumulative monthly and annual statistic reports are to be maintained but not dwelled upon to the exclusion of staff interest.
- E. Assignment of responsibility should be done only to promote interest and to institute corrective measures.

Definitions*

- I. Classification of fetal and neonatal death
 - A. Fetal death: Death prior to complete birth, irrespective of the duration of pregnancy.

^{*}Adapted in part from "A Guide for the Study of Perinatal Mortality and Morbidity" published in 1959 by the Committee of Maternal and Child Care of the Council on Medical Service, The American Medical Association.

- B. Neonatal death: Death after complete birth but prior to the twenty-eighth day of life.
- C. Perinatal death:
 - Period I: Fetal and neonatal deaths of infants over 1,000 grams (2 pounds, 4 ounces) occurring in the first 7 days of life.
 - Period II: Fetal and neonatal deaths of infants over 500 grams (1 pound, 2 ounces) prior to the twentyeighth day of life.

II. Time of death relative to labor

- A. Antepartum: Fetal death before labor.
- B. Intrapartum: Fetal death during labor.
- C. Neonatal (postpartum): Fetal death occurring after labor but prior to the twenty-eighth day of life.

III. Death based on length of gestation

- A. Abortion: 500 grams or less or less than 20 weeks after the last menstrual period.
- B. Premature, previable: 500 grams through 1,000 grams.
- C. Premature: 1,001 grams through 2,500 grams (5 pounds, 8 ounces).
- D. Term: Over 2,500 grams.
- IV. The perinatal mortality rate is calculated on the total number of births as compared with the number of deaths in a given time period
 - A. Perinatal Period I rate = fetal deaths 1,001 grams and over divided by live births and fetal deaths 1,001 grams and over multiplied by 1,000.
 - B. Perinatal Period II rate = neonatal deaths and fetal deaths 501 grams and over divided by live births and fetal deaths 501 grams and over multiplied by 1,000.
- V. Perinatal morbidity: A pathologic condition observed in the fetus or infant during the perinatal period.

It is hoped that, in the future, perinatal mortality committees will also review cases of morbidity. Many infants grip tenaciously to life almost in spite of us. Much can be done to improve the care of the newborn by reviewing conditions leading to morbidity.

Results

A perinatal mortality study should result in the unification of all the hospital services for improved pediatric and maternal care. The aims should be as follows: (1) complete case study; (2) exchange of ideas; (3) severe self-criticism; (4) reappraisal of management; (5) medical education.

The dangers

The inherent danger in a perinatal mortality study would be the massing of foolish statistics. It does little good simply to pile statistics one upon the other.

Certainly nothing could cause more disunity in an obstetric department than to have personality clashes regarding the management of the case. This is not the purpose for the organization of a perinatal study. Only by cool, calm deliberation in regard to the outcome of any given case could a careful analysis yield a better method of management.

Finally, one would say that in all cases the reports should be confidential in order to remove the possibility of medicolegal action to those parties involved. In some states, such as Ohio, we have specific laws covering the records of such committees. The law permits the discussion of the attending staff to be entirely off the record as far as the chart is concerned.

Representative forms for case reporting

As indicated above, the massing of statistics or police action should not be the purpose for the existence of a perinatal mortality committee. The welfare of the given patient is the essence behind all such studies. The modern trend to categorize everything is well known. Sometimes this leads to misinformation. Nesbitt³ evaluated the extent to which death certificate diagnoses vary from autopsy findings in 1953 at The Johns Hopkins Hospital. The certificate diagnoses varied in 40 per cent of the cases from pathology diagnoses.

The agreement was even less impressive, 32 per cent, for a similar investigation of deaths that occurred during the first 2 weeks 161

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1. Voluntary. Involvement by the physician concerned produces the greatest educational benefits.

2. Local. The only persons really qualified to evaluate cases of perinatal mortality are those who are entirely familiar with the local conditions.

3. Current. The extreme brevity of most newborn records demands the investigation of the cases of a current basis for accuracy.

of life. The details of an effective method of collecting pathologic diagnoses need to be investigated. In many communities this information could be secured by requesting pathologic data in all cases where the certificate indicates an autopsy was performed.

Summary

The success of the program depends in turn upon the approach with which it is undertaken.

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Discussion

DR. James Hutchison Williams, Columbus, Ohio. The problem of perinatal mortality can be approached in either of two ways: (1) by fundamental investigation and basic research; (2) by clinical investigation aimed at better management of patients in the areas wherein we already know of the means to better results. These might well be termed the "ivory tower" and the "grass roots" methods, respectively, and I should like to illustrate each of these approaches by an example with which I have close personal contact.

1. There has recently been established at the Ohio State University an Institute for Perinatal Studies. This institute has attracted interested members from the basic as well as the clinical departments of the College of Medicine, and from the Colleges of Dentistry, Veterinary Medicine, and Pharmacy as well. Since perinatal mortality and morbidity studies have much more far reaching implications than those of the medical sciences alone, the College of Agriculture with its School of Home Economics, the College of Commerce and Administration with its Department of Social Sciences, and the College of Education with the Department of Psychology have joined forces with us. This has resulted in a number of new avenues for research effort and will soon include advances in adult education as well. This is one example of an "ivory tower" approach.

2. At the same time, education on the physician-patient level can decrease the 25 per cent of perinatal deaths which may have some factors of preventability. This is illustrated by the following data from the current Franklin County (Columbus, Ohio) Perinatal Mortality Study (Table I).

Table I

Hospital	NP*	P_{I}	P_z
A	73%	11%	16%
В	83%	2%	15%
C	73%	10%	17%
D	85%	5%	10%
E	81%	3%	16%

 $^{8}NP = No$ preventable factors; $P_{1} =$ patient responsibility factors; $P_{2} =$ personnel management factors.

These data are the result of voluntary, local, and current`studies in the individual hospitals. Reporting has varied from a small number to 100 per cent of cases, and the autopsy rate has varied from 10 to 90 per cent autopsies on perinatal deaths. In each instance, however, the staff concerned, evaluating its own cases, has come up with strikingly similar results. In each hospital, self-recognition of improved possibilities has been realized. It is hardly necessary to state that as a result, in each one of these hospitals, there has been recognizable improvement

in obstetric management, particularly in labor and delivery.

As Dr. Holzaepfel has concluded, continued investigation of basic causes can and must be enlarged. This is best achieved in centers where basic research is already at work or can be developed. This is not directly the mission of the Central Association. Collection of mass statistics is helpful, too, but has been done in many areas. The errors of later evaluation of detailed questionnaires, unless they are clinically interpreted locally and currently, is well-known to us all.

Arthur King,¹ in his paper on perinatal mortality, presented before this society one year ago, concluded, "Even a poorly equipped, nonaccredited hospital can show an excellent fetal salvage rate if it has good staff discipline in regard to obstetrical consultation, analgesia, and anesthesia, and prompt, expert pediatric care." Edith Potter,² has stated in part that ". . . the greatest benefit from any study is derived by the people most intimately concerned with it. . . . It is much more valuable for us to discover our own weaknesses than to have others point them out." The sense of these statements taken together would seem to equal "voluntary, local, and current."

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Dr. D. N. Danforth, Evanston, Illinois. In connection with the mechanism by which such cases can be reviewed, I wish to mention a device which has greatly facilitated our own deliberations on perinatal mortality at the Evanston Hospital. This is a modification of the classi-

fication outlined by Kendall and Rose (Pediatrics 13: 496, 1954), in which each case must be categorized in each of three ways. The first category designates the medical service to which the death is to be charged: (A) obstetrics, (B) pediatrics, (C) surgery, (D) combined. The second category relates to preventability and requires that a decision be made as to whether the death was (I) preventable, (II) nonpreventable, or (III) unclassifiable with regard to preventability. The third category identifies the direct reason or responsibility for the death: (1) inadequate prenatal care, (2) family at fault, (3) physician—error in judgment, (4) physician—error in technique, (5) intercurrent disease, (6) unavoidable disaster, and (7) anomalies incompatible with life. According to this classification, a stillbirth resulting from premature separation of the placenta would be classified as A-II-6. The decisions regarding each case are made at the monthly departmental meeting by the entire department. All cases having preventable factors are then submitted, without identifying data, to the Suburban Cook County Committee on Maternal and Infant Health for consideration and discussion, along with similar data from 12 other participating hospitals.

An occasional case arises which cannot be fitted precisely into these groupings, but this does not diminish the usefulness of the classification. Its primary advantages are, first, that it requires a detailed review of all pertinent data regarding each fatality and, second, that it permits easy analysis and grouping of long-term results.

DR. HOLZAEPFEL (Closing). I would re-emphasize only that we feel the main thing to do is to get started regardless of how the committee may be organized at first. We have made up these forms only in order to assist in any way we might.

The epithelium-stroma junction in the uterine cervix

Histologic and electron microscopic studies

CARY M. DOUGHERTY, M.D.

Baton Rouge, Louisiana

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THE basement membrane underlying the epithelium of the cervix, it is commonly believed, is the key to determining the state of invasion, or absence of it, in early cervical carcinoma. The practical difficulty has been simply that two experienced observers looking at the same specimen in the same place often disagree as to its preservation, one seeing it intact, the other noting it to be broken. Almost without exception every author writing about carcinoma in situ in the last decade has emphatically cited the basement membrane in the definition of that entity or has pointed out in illustrations the containment by or the breaking through of this elusive barrier.

Broders¹ seems to have experienced misgivings which should have put later observers on guard when he stated in defining carcinoma in situ that "[carcinoma cells] have not migrated beyond the junction of the epithelium and connective tissue or the so-called basement membrane. . . ." Stevenson and Scipiades² were bolder in their description of "non-invasive potential 'carcinoma'

of the cervix" in noting ". . . it may break through the basement membrane and invade and destroy the stroma of the cervix, having then become clinically a cancer." Meyer3 probably gave the greatest impetus to the concept when he wrote regarding early carcinoma of the cervix, "the carcinoma continues its proliferative course, breaking through the basement membrane of the gland to invade the underlying tissue. It does not require the gland for direct invasion but uses it on occasion as a matter of convenience. . . . The basal membrane is often intact in the early stages [of carcinoma] and is destroyed as the disease advances." Repeated references to the membrane hypothesis by this authority appear: "'. . . the basement membrane is still intact and sharply separates the epithelium from the connective tissue,' '. . . and here the basement membrane is quite indistinct,' '... the epithelium surrounding the large papilla is irregular with defects in the basal membrane.' '. . . The basal membrane is fading, damaged in all probability by the toxic influence of the carcinoma cells.' '. . . [the carcinoma] had remained superficial, perhaps as a result of the exceptionally strong membrana propria.' "4

Foote and Stewart⁵ mapped the growth of intraepithelial and early invading carcinomas of the cervix and remarked, "The infiltration referred to was extension of the tumor beyond the basement membrane. . . . TeLinde and Galvin applied the term 'invasion' to extension below the surface epithelium and

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into the lower-lying cervical glands and did not use it in the sense of an extension beyond the basement membrane with actual infiltration of the fibromuscular stroma of the cervix." Dr. Emil Novak6 examined the question by using the subjunctive form of statement: "If one can actually demonstrate a breakthrough of the basement membrane, with free penetration of cancer cells, . . . there will be no difference of opinion among pathologists as to the invasiveness of the lesion. . . ." These references and many, many others including the works of Epperson and associates,7 Bechtold,8 Friedell,9 Huey,10 Hahn,11 Morton,12 Galvin, Jones, and Te-Linde,13 and Limburg14—the great preponderance of written reports-indicate that the investigators rely on identifying the correct state of repair of the membrane in judging whether a given growth is surface or invasive.

A modification of this concept, though not fundamentally different, is typified by the observations of Schiller. The membrane is not considered to be so important: Let corium has a nonspecific arrangement of connective tissue bundles and a network of argentaffine fibers . . . demonstrable by . . . Bielchowsky stain. The network formed by these fibrils shows areas of condensation. . . One area of condensation is at the junction between the basal layer of the epithelium and the upper margin of the corium. This layer of apparently increased density is erroneously accepted as a special structure, which it definitely is not."

Allen¹⁶ concluded that stratified squamous epithelium of the skin rests directly upon the connective tissue without a basement membrane. Though not exactly the same as mucous membrane epithelium, the epidermis is structurally similar and could be expected to bear the same relationship to corium as does the mucosa.

From this résumé it can be seen that most investigators believe they see a basement membrane beneath the cervical mucosa, and most state that they use this marker to determine whether early cancer is contained in the surface layer or whether it invades the stroma. Further, there is a minority who

are strongly convinced that the membrane is of no practical value. It would seem advisable, therefore, to study directly this vital zone.

Method of study

For the first part of the investigation several hundred cervical biopsies obtained from patients in the Louisiana State University Gynecological Clinic were sectioned and stained with hematoxylin and eosin, PAS, and reticulum stains. Specimens illustrating normal epithelium, erosion healing, epithelial atypism (basal cell hyperactivity, anaplasia, dysplasia), carcinoma in situ, and invasive squamous cell carcinoma were used. No attempt was made to secure samples of disease consecutively but rather specimens were selected for their good technical quality and their representation of the typical lesion in each category.

Histologic diagnosis was recorded after examining the hematoxylin and eosin sections. With PAS sections an effort was made to trace the basement membrane as a thin line (the profile of a sheet) between the epithelium and connective tissue. A positive identification was a pink or red line, the Schiff reaction of the ground substance of the basement membrane. Reticulum stain for connective tissue fibrils brought out the fibrillar component of the membrane.

Other stains were tried, among them the phosphotungstic acid-hematoxylin stain and various modifications of the silver impregnation stains, but these did not aid further in interpretation of structure.

In the second part of the study specimens of normal cervix and of known cancer tissue were secured for electron microscopy. In patients with proved cancer of the cervix small pieces of tissue were removed and each was divided lengthwise into electron study specimen and control specimen for light microscopy. The first half was fixed in osmium tetroxide, embedded in methacrylate, and prepared by ultrathin sectioning. Paraffin sections stained as in Part I were made from the second half of tissue. Magnification of photomicrographs was measured directly

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Observations

Part I. Fig. 1 illustrates carcinoma in situ with the standard hematoxylin and eosin stain. Fig. 2 pictures the same area of tissue stained with PAS. There is a thin pink line beneath the epithelium continuous in every place except at the apex of the connective tissue papilla, where there is an indistinct fuzziness. The general finding in practically all of the specimens of carcinoma in situ was similar: a faint red line beneath most but by no means all of the epithelium affected. There were breaks or missing portions of this line in specimens in locations where the disease was unquestionably limited to the surface. Moreover, it was commonplace to see long projections of epithelial growth budding from the basal part of the epithelium contained by a basal membrane. Beneath most carcinomatous extensions along columnar epithelial (gland) surfaces a definite lamina could be identified, but this observation did not hold for all areas of gland extension. In certain places definite balls of carcinomatous gland extensions of in situ disease exhibited no sign of a membrane.

Many biopsy specimens from clinical carcinomas showed details diametrically opposite to that anticipated by the basement membrane hypothesis. One of these carcinomas (Fig. 3) possessed a clear, intact membrane in both the PAS stained section (Fig. 4) and the section stained for reticulum (Fig. 5).

Since the basement membrane should be reliably present in the one stage of disease and completely absent or broken up in the other, no count was made of the times that exceptions were noted. It would be a safe statement to make, however, that there were few carcinomas in situ where the membrane could be traced completely intact, and there were many invasive growths in which more or less long stretches of membrane were seen beneath and around masses of cancer tissue. Part II of the study was undertaken when it was seen that the light microscope could not resolve the question.

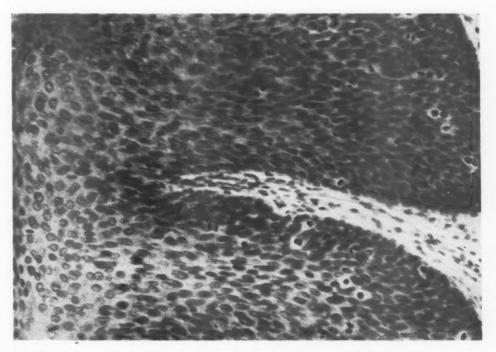
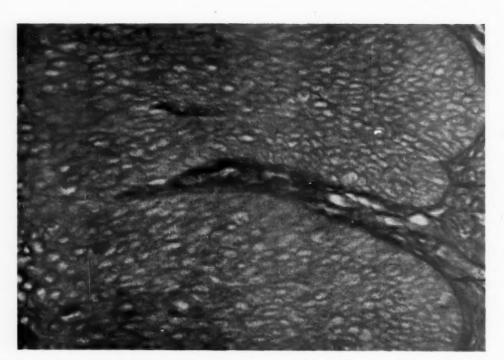


Fig. 1. Carcinoma in situ. (Hematoxylin and eosin. Original magnification ×340.)



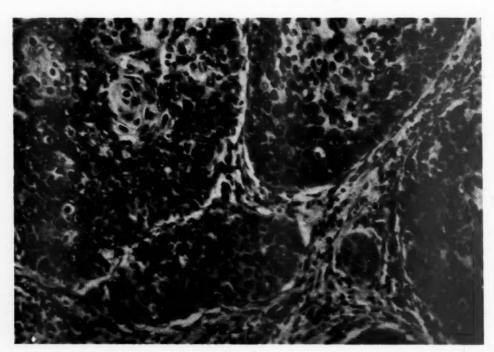


Fig. 3. Squamous cell carcinoma. (Hematoxylin and eosin. Original magnification ×340.)

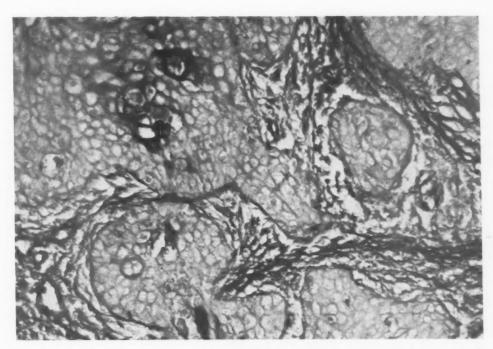


Fig. 4. Squamous cell carcinoma, same tissue block as in Fig. 3. Clearly visible "membrane" surrounds most of carcinoma masses. (PAS. Original magnification ×340.)

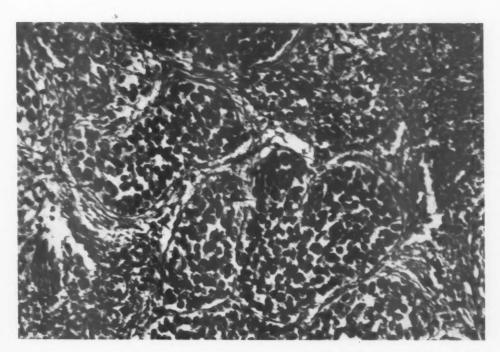


Fig. 5. Squamous cell carcinoma, same block of tissue as in Fig. 3. Definite reticulum-positive "membrane" encloses masses of carcinoma tissue. (Reticulum stain. Original magnification ×340.)



Fig. 6. Electron micrograph mosaic of normal cervical epithelium. Arrows indicate connective tissue junction and the exomembrane. ep = Epithelial cell; et = connective tissue; nue = nucleus; mi = mitochondria; pr = protomembrane; pe = perimembrane; exm = exomembrane. (Total original magnification $\times 36,600$.)

Part II. There was no particular difficulty encountered in recognizing the junction of epithelium and connective tissue in the preparations of cervical tissue. Because of the small fields of specimen viewed at one time and because of the different staining characteristics, it was not so easy to recognize disease in the electron microscope sections. The control half of each tissue prepared for the light microscope was used to identify both disease and orientation.

Fig. 6 is an electron micrograph of normal cervix. This illustrates the detail of relationship of epithelium and stroma which have been found to exist in all specimens of normal cervix so far examined.17 The junction is marked by a double-layered structure apparently made up of the cell plasma membrane on the epithelial side, an electronlucent component between, and a thin, dark layer on the connective tissue side. This arrangement is typical of basement membrane in many locations as observed in electron microscopy. The same structural detail is also seen in some situations where light microscopy does not reveal a basement membrane.18 A special terminology has been assigned to this structure by Lindner,19 and later by Poche.20 They designate the whole complex the exomembrane, the dark line on the epithelial side the protomembrane, and the outer layer at the connective tissue space the perimembrane. Thus, the protomembrane and the perimembrane, with the clear interspace between them, constitute the exomembrane.

Another significant finding on the electron micrographs is that there is no condensation of connective tissue fibrils immediately subjacent to the exomembrane, nor is there an accumulation of so-called ground substance. In short, there is nothing which could be stained and seen with the light microscope.

In Fig. 7 the junctional relationship in carcinoma in situ is seen. There is no difference in the structure of the exomembrane here and in the normal cervix. It is literally intact on this specimen as far as it could be traced, with no sign of break or dis-

solution. As in normal tissue there is no densification of the connective tissue beneath the epithelium or special arrangement of fibrillar material which could be demonstrated by light microscopy.

When specimens of cervix containing known cancer disease were viewed by electron microscopy no constant junctional structure could be found.21 Several explanations for this observation were considered. Artifactitious changes produced by osmication or improper fixation of carcinomatous epithelium could account for an indistinct border. Improper orientation of the tissue when sectioned may result in a tangential cut with fuzzy epithelial lines. However, these difficulties are commonly encountered in paraffin sectioning and with due care they can be compensated. It is felt that similar compensation can be made in the use of the newer modality.

A third and most likely correct explanation for the inconstancy of junctional structure is the inherent variability of cancer growth. This is a characteristic of ultrastructure of cancer cells as well as organelles within cancer cells.22, 23 In one carcinoma specimen a complete exomembrane was found (Fig. 8). It was in every way like the one occurring in normal tissue. In another area a membrane was found to have breaks in continuity (Fig. 9). Many junctional zones exhibited only cell wall or plasma membrane adjacent to connective tissue (Fig. 10). Probably the most frequent observation was that where the carcinoma border was indistinct and without the sharp detail found to be characteristic of normal tissue. This type border is seen in Fig. 11. Of course, it is not possible to say whether there is a membrane in these regions. One could surmise there is not. In a few specimens junctional epithelial cells exhibited a microvillous pattern on the connective tissue side. This pattern is thought to be characteristic of intermediate or superficial cells. In these areas there was no structure other than the cell plasma membrane (protomembrane) between epithelium and connective tissue (Fig. 12).

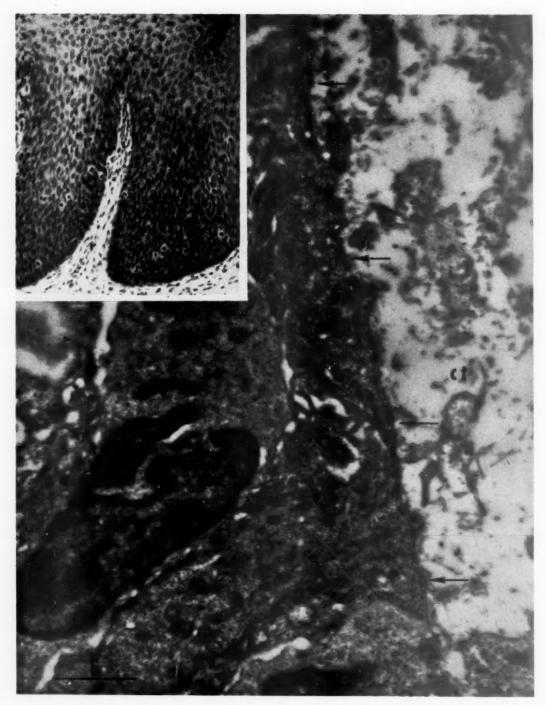


Fig. 7. Electron micrograph of carcinoma in situ with inset showing hematoxylin and eosin section. Arrows indicate intact exomembrane. (Total original magnifications $\times 28,400$ and $\times 170.$)

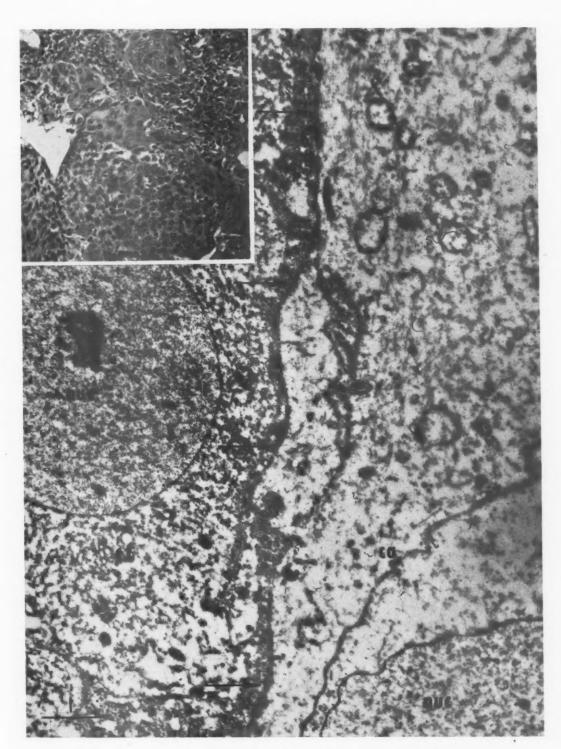


Fig. 8. Squamous cell carcinoma, light and electron microscopy photographs. The exomembrane is the same in this as in the specimen in Fig. 7. (Total original magnifications $\times 21,200$ and $\times 170.$)

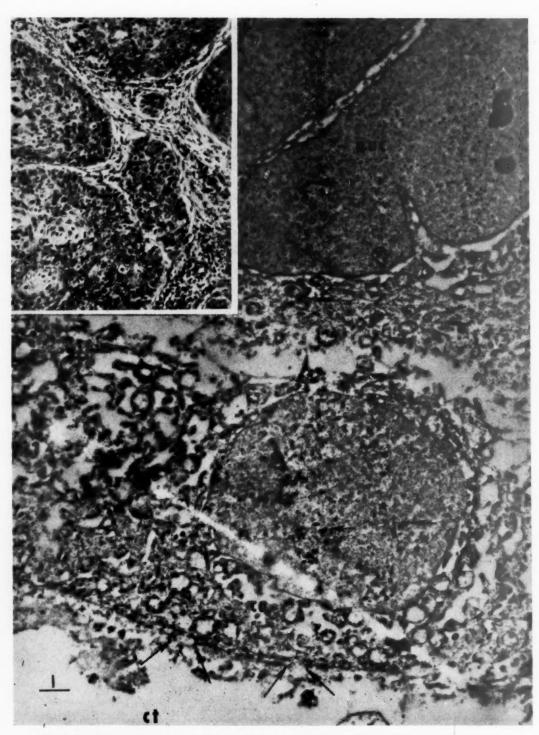


Fig. 9. Squamous cell carcinoma, light and electron microscope photographs. Arrows at bottom indicate discontinuity in the exomembrane. Irregular chromatin masses in nuclei, indicated by arrows above, are similar to virus bodies found by other investigators (see text). (Total original magnifications ×10,500 and ×170.)

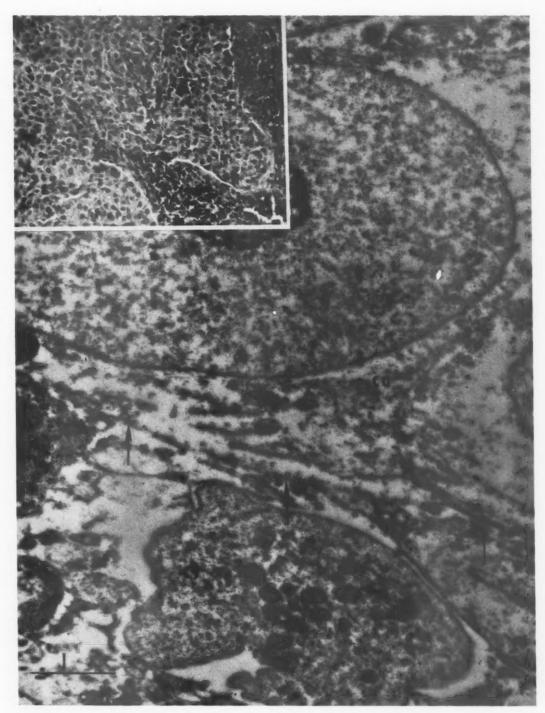


Fig. 10. Squamous cell carcinoma, light and electron microscope photographs. Junction of carcinoma cell is limited by plasma membrane only (protomembrane). (Total original magnifications $\times 28,400$ and $\times 170.$)



Fig. 11. Squamous cell carcinoma, same specimen as in Fig. 10. Border of carcinoma cell is indistinct. (Total original magnification $\times 28,400.$)

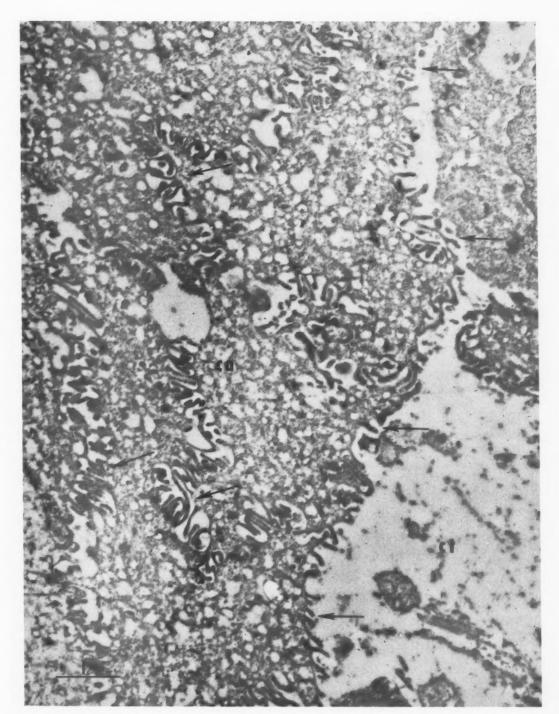


Fig. 12. Squamous cell carcinoma, same specimen as in Fig. 8. Microvillous pattern at periphery of cells and at junction with connective tissue space. (Total original magnification $\times 21,900.$)

There were two additional features seen in some of the cancer cells examined by electron micrography which are worthy of comment. These observations would seem to suggest the possibility of virus development within these cells. Dense condensations of nuclear chromatin material indicated by arrows in Fig. 9 are similar to those observed by Morgan and associates,24 who believed them to be related to formation of intranuclear crystalline virus bodies. Second, a complicated meshwork of microvilli at the periphery has been observed to be a feature of cancer cells in this study (Fig. 12) and in culture²⁵ and in cervical carcinoma.²⁶ It has been suggested by Bernhard that viruslike particles are transferred from intracellular to extracellular positions and forms through the medium of the microvillus system.

Conclusions

1. A basement membrane cannot be demonstrated with consistency beneath the cervical epithelium in normal or carcinoma in situ specimens by the use of light microscope and specially stained paraffin tissue sections.

- 2. A structure resembling a basement membrane can sometimes be shown to be in position under masses of carcinoma tissue, using the same method of examination.
- 3. An exomembrane, consisting of an inner protomembrane and an outer perimembrane separates epithelium and connective tissue of the cervix in a constant relationship in electron microscope specimens.
- 4. The exomembrane delineates some but is missing from most carcinoma epithelium in electron microscope preparations of cervix.
- 5. Two features suggesting the possibility of viral development within the cells were noted in this study of cancer cells. One was the presence of dense clumps of nuclear chromatin material, the other was formation of microvilli at the cancer cell periphery.

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Discussion

DR. Kenneth E. Cox, Kansas City, Missouri. In this and previous publications, Dr. Dougherty has demonstrated that the ultramicroscopic "exomembrane" is a continuous and intact anatomical structure separating the cervical stratified and columnar epithelia from the underlying stroma.

In carcinomatous epithelia, he has demonstrated that the exomembrane may be intact, but is usually absent, or in certain loci may have an indistinct or fuzzy appearance possibly denoting the advancing edge of cancer. In still other situations a complex microvillous pattern of the cell membrane of cancer cells marks the boundary between cancer cells and stroma. This latter feature along with dense aggregations of granular material within the nuclei suggest to him the possibility of viral development within the cells.

From the clinical point of view, these findings will have a tremendous effect on our appreciation of the pathogenesis of cancer with respect to probable viral etiology, host resistance, and correct appraisal of the significance of "in-situ" and "microcancer" stages of cervical cancer.

On the basis of clinical observation and careful follow-up, most observers today believe that equivocal or very early stages of so-called "microscopic invasion" should be managed conservatively, i.e., wide conization or simple total hysterectomy with careful follow-up, and preser-

vation of the ovaries when desirable. Dr. Dougherty's work corroborates these clinical opinions. The microscopist may now better appreciate the vagaries of "basement membranes" visible under the light microscope. As he reviews the multiple slides presented to him from a cervical cone where the gross lesion was minute if visible at all, he will better evaluate the evidence before him; and perhaps, if the postulations made in this presentation with respect to viral activity are shown to be factual, he may experience a deeper understanding of the battle that is taking place at ultramicroscopic levels between the host and the invading cancer.

Dr. Dougherty (Closing). We must look at some of these findings with the thought that we may be observing processes the nature of which we have no conception at present. We cannot make all of our observations fit into our present knowledge.

The use of the basement membrane as a criterion of invasion in paraffin sections is not valid. It simply cannot be done. The best guess as to what you are seeing on reticulum stain is that a layer of stain is precipitating around the bottom of the epithelium. It may be the same in the PAS and hematoxylin and eosin stains as well. Rather than an actual structure, you may be looking at an artefact. We cannot compare directly the light microscope preparations and the electron microscope preparations.

Detection and disposal of breast cancer in pregnancy

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IN SEVERAL previous papers the author and co-workers have pointed out the important role which the specialist in diseases of women may play in the diagnosis and management of diseases of the breast. The fact has been recognized that there has been no improvement in mortality statistics of cancer of the breast in the past 25 years while during the same time there has been a dramatic fall in the death rate from cancer of the uterus, and the obstetrician and gynecologist has been urged to devote the same meticulous attention to reaching an early diagnosis of breast carcinoma as he now employs in the diagnosis of carcinoma of the cervix and of the endometrium. It is believed that if examination of the breast is incorporated in all gynecologic examinations and if small and questionable lesions of the breast are subjected to biopsy as frequently as curettage and biopsy are done in suspicious lesions of the womb, perhaps the same effectiveness of control may be achieved in this field as in that of carcinoma of the uterus.

During the course of previous presentations we have intimated our views concerning the special problem of breast disease in pregnancy but have never devoted to this problem the full attention which it merits.

In order to identify the scope of this additional problem I wish to present statistics from the Committee for the Study of Breast Cancer of the Philadelphia County Medical Society of which I am a member (Table I). In a period of approximately 10 years, 5,709 cases of breast cancer have been collected of which 4,956 have been subjected to critical review. Among the latter group there were 650 who were under 40 years of age, bringing to light a very considerable number of young women in whom the disease might well have developed or have become accentuated during pregnancy. Actually 70 cases were found in which disease was detected either during pregnancy or in the 6 months immediately thereafter. These 70 cases constituted 1 in 70 of the total number of patients with breast cancer material in 1 in 9 of the patients under 40 years of age.

Table II reveals the circumstances related to diagnosis and therapy of this special group. For purposes of comparison the cases have been divided into a first and a second period. Rather consistently throughout the entire series the disease was found by the patient herself (approximately 90 per cent) in spite of the fact that most of these patients were coming regularly to the obstetrician for prenatal and postnatal care. Failure to examine the breast, misinterpretation, or belittling of the physical findings resulted in delay in tissue diagnosis on the

From the Department of Obstetrics and Gynecology of the Jefferson Medical College.

Guest Speaker's Address, presented at the Twenty-eighth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Kansas City, Missouri, Oct. 6-8, 1960. part of the physician in approximately 60 per cent. The group in which the patient carried the onus of delay was much smaller.

Metastasis was found to be present at time of operation in 74 per cent of the first 5 year series. In 20 per cent of these, metastasis were systemic in distribution. The one salutory phase of comparing the first and second series was the reduction in rate of metastasis to 28 per cent in the latter.

Where follow up was available for the first 5 year group 45 per cent were found to have died in less than 2 years and 66 per cent within 5 years. When these statistics are complete the mortality figure will undoubtedly be higher.

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Source of detection. It is well known that in the past most breast lesions have been noted first by the patient during accidental or unguided palpation of the breast. This situation seems to continue in very considerable part up to the present. In 90 per cent of this group occurring in pregnancy the lesion was found first by the patient; in only 10 per cent by the physician.

It seems hardly reasonable for this situation to exist when a patient is pregnant and making regular frequent visits to the obstetrician for prenatal and postnatal care. If the obstetrician were to include examination of the breast not only in his first physical examination of the patient but in the subsequent checkups he should be the first to note significant disturbance in this area.

When examination of the breast is done regularly and faithfully as a part of each gynecologic and obstetric examination the physician should be and will be the first to notice suspicious lesions. Recently we reported on 3,608 consecutive private patients in whom at various times 819 suspicious or questionable areas of the breast were noted. Only 98 of these suspicious areas had been found by uninstructed patients, 67 had been found by patients instructed in self-examination, and the remaining 644 were detected in examination by physicians of our group.

It is an unfortunate commentary on the activities of the physician when lesions of the breast have to be called to his attention by a patient who is making regular visits to his office for checkups during pregnancy.

Delay in diagnosis by the physician. In the same vein it is equally distressing to find that in 60 per cent of these pregnant patients the physician was responsible for delays in diagnosis, some of which extended for 3 months up to 3 years. In this situation the physician either failed to examine the breast where obvious lesions of very considerable size were detected or he had viewed

Table I. Total cases in Philadelphia breast cancer study

Years	Serial No.
1951-1952	1- 245
1952-1953	246- 527
1953-1954	528-1,015
1954-1955	1,016-1,758
1955-1956	1,759-2,462
1956-1957	2,463-3,318
1957-1958	3,319-4,125
1958-1959	4,126-4,956
1959-1960	4,957-5,709
Cases completely reviewed	4,956
Number under 40 years of age	650
Cases detected in pregnancy	
or 6 months thereafter	70
(1 in 70 of total material)	
(1 in 9 of patients under 40	years old)

Table II. Factors in diagnosis and results in carcinoma of breast in pregnancy

-	First 5 years	Second 5 years
Number	42	28
Found first by patient	38 (90%)	24 (86%)
Found first by physician	4 (9+%)	4 (14%)
Delay in diagnosis by physician	28 (66%)	13 (46%)
Metastasis present at op- eration	31 (74%)	8 (28%)
A. Regional	23 (54%)	7 (25%)
B. Systemic	8 (20%)	1 (3%)
Survival less than 2 years	19 (45%)	4(?)
Death from cancer	28 (66%)	5
No follow-up	8	23
Living with or without disease	6	

lightly the concern of the patient herself regarding the lesion which she had discovered and passed it off as an innocuous situation.

The histories of these cases are replete with such statements as:

"Failure of physician to examine breasts during pregnancy even though the patient complained of distress."

"Surgeon to whom patient was referred, repeatedly called the lesion 'cystic disease.'

"Physician did not biopsy lump."

"This prenatal clinic does not practice routine examination of breasts in pregnancy."

"Lesion treated with hot compresses and penicillin."

"Patient told it was a milk duct."

"Recheck breast after pregnancy is over."
Apparently in many areas the proposition of performing a biopsy of the breast is considered a very formidable undertaking which should not be attempted in the course of pregnancy. Actually in the entire 70 cases there were only 17 in which there was no delay in reaching histologic diagnosis.

The physician delay of 90 per cent in the instance of breast cancer in pregnancy is quite in contrast to the 29 per cent delay which is noted in the over-all study of breast cancer for the same period of years. These figures suggest that there is a more difficult problem in diagnosis in pregnancy than in nonpregnancy, and possibly this is true. However, from the cases recorded in this study, there seemed to be no doubt that a recognizable lesion of the breast existed. The delay in diagnosis appeared to derive from 3 sources: (1) failure to realize that breast cancer occurs during pregnancy; (2) failure to examine the breast regularly; (3) failure to biopsy promptly when a lesion was found.

The error in 90 per cent or more of these cases could have been avoided if these principles had been kept in mind.

Metastasis at operation. The result of this delay in concrete histologic diagnosis was an over-all rate of metastasis at the time of operation of 56 per cent and a systemic metastasis rate at the time of operation of 20 per cent. These figures point up the rapid growth and extension of breast cancer and also the profound effect which delay in diagnosis have upon its extension.

Actually, the data for the later years were gratifyingly better than in the first 5 years of analysis, and it is hoped that in Philadelphia the efforts of the Breast Cancer Committee will be rewarded by increasing consciousness of cancer in the pregnant patient.

While figures for delay on the part of the physician in the second period of study did not seem much better than in the first, the bare statistics do not reveal the tremendous reduction in the length of individual delays.

Survival rates. Results are known for only 34 of the 42 cases in the first 5 years but these again reveal the tragic results of the disease itself and of delay in recognition.

Most writers on this subject believe that if early diagnosis can be effected the survival rate will be comparable with that of the nonpregnant patient in the same age period.

Types of lesion encountered and histologic diagnosis. The presence of pregnancy undoubtedly has some effect upon the clinical characteristics of breast disease. For instance in the case of chronic cystic mastitis the lesions seem to meld into the general enlargement of the breast during pregnancy and become less palpable and less significant.

Fibroadenomas, on the other hand, remain quite clearly palpable and freely moveable and usually enlarge with the general hyperplasia of the breast.

Breast cancer itself may be somewhat less clearly defined and more difficult to palpate. However, such lesions do not become obscure, and careful examination and reexamination will assure the examiner of significance in his findings.

Inflammatory carcinoma is frequent in pregnancy and was encountered in 3 cases of this series. In each instance the disease was thought to be mastitis and was treated with antibiotics and warm compresses.

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real problem in the histologic diagnosis of breast lesions in the pregnant state. Aside from the hyperplasia of adjacent breast tissue and the slight edema there is no real difference.

Frequency of breast disease and general significance of the problem. Judging from experience in ward and private practice, one is likely to encounter one significant breast lesion in every 100 pregnant patients who are previously unscreened for breast disease. In private practice where many of the pregnant patients have been observed between pregnancies and significant lesions of the breast removed, the frequency is less. About 1 in 10 or less of these lesions will prove to be cancer.

In the period of time of the intensive phases of the breast study in Philadelphia there were approximately 420,000 deliveries or an occurrence rate of 1 in 4,000. It is quite probable that not all the breast cancers in pregnancy were caught in this study just as not all of the breast cancers in general were included, and the figure may well reach 1 in 2,000 or 1 in 3,000.

The question may be asked then: "After all, how much of a problem is this for the obstetrician with his many other concerns for maternal morbidity?" The reply is simply that an important differential diagnosis of breast disease arises in about 10 of each 1,000 gravid patients and in one of these an extremely grave or fatal disease may be overlooked. This one case may constitute 30 to 50 per cent of maternal mortality in a given area. While this mortality from breast disease does not appear at the moment on the obstetrician's side of the ledger, yet I think it may be agreed from what has been said above that it may rightfully belong there.

Disposal of breast lesions found in pregnancy. I cannot leave this subject without saying something concerning the general management and disposal of breast lesions found in pregnancy.

There probably will be little disagreement in an intelligent body of physicians with the policy of biopsy and tissue study whenever a breast lesion is found during the course of pregnancy. As to how this procedure is done, as to what relationship the diagnostic procedure may bear to ultimate definitive operations, and as to what should be done about the pregnancy in the face of cancer of the breast, there may be considerable difference of opinion.

We have always felt the first and most important thing to do is the biopsy. Second we feel that the biopsy should be done in as atraumatic a fashion as possible and in this particular instance as a procedure separate from the ultimate operation. Accordingly, we have set up at Jefferson a policy agreed to by the Department of Surgery and the Department of Obstetrics that all patients having a significant lesion of the breast shall have a preliminary biopsy performed under local anesthesia. The performance of such does not subject the patient or the fetus in utero to hypoxia and does not immediately force the surgeon's hand as to what he should ultimately do about the situation.

If by chance the biopsy indicates the presence of cancer then of course the decision must be made regarding the disposal of pregnancy and the time of ultimate mastectomy. In view of the extremely serious nature of carcinoma of the breast and the profound effect which the enhanced circulation and the stimulus of hormones have upon growth of this lesion, we feel that pregnancy should be promptly terminated. If the patient is within the period of viability, a living fetus may be salvaged. If not, the embryo is sacrificed. If carcinoma is extensive, it is well to terminate the pregnancy by abdominal section, hysterectomy, and bilateral salpingo-oophorectomy.

Third, we believe that in this situation there is a firm indication for preoperative x-ray therapy. The x-ray therapy given in full course reduces the circulation of the breast, inhibits the growth, and may help to seal lymphatics. Radical mastectomy is performed some 6 or 8 weeks after the beginning of x-ray therapy.

Personal cases of carcinoma of the breast

in pregnancy. No one person and comparatively few clinics have had any extended experience in the therapy of carcinoma of the breast in pregnancy. My own contact has been with 5 cases, as follows:

Case 1. Seen in consultation in 1944, the patient had felt a lump during the latter part of pregnancy but had neglected to call it to the attention of the obstetrician. During the immediate puerperium in the hospital she mentioned the matter to him. An obvious lesion some 3 cm. in diameter was noted in the upper and outer quadrant which was biopsied under local anesthesia and was found to be an intraduct carcinoma. Preliminary x-ray therapy was administered which was followed in 6 weeks by radical mastectomy. There were no metastasis to the axillary glands. The patient has continued alive and apparently free of disease.

Case 2. A 39-year-old patient came to the office with an obvious lesion of the breast for which biopsy was recommended. She postponed this procedure and came back in 3 months with early pregnancy. This time she accepted treatment and incisional biopsy under local anesthesia revealed the presence of scirrhous carcinoma. The uterus was emptied by abdominal hysterotomy, and preliminary x-ray therapy of the breast was administered. Six weeks later a radical mastectomy was performed and no axillary gland involvement was noted. This patient survived 11 years and died of acute lymphatic leukemia.

Case 3. Delivered 2½ months previously 1 an adjacent city, the patient had noticed a nodulation in the upper and outer quadrant of the breast. Biopsy revealed a mucocarcinoma of the breast, and radical mastectomy was performed under the same anesthesia. No axillary gland involvement was noted. In view of the stimulating effect of the recent pregnancy the radiologist advised postoperative x-ray therapy and bilateral oophorectomy. Since this patient was a young woman the oophorectomy was not performed but the postoperative x-ray therapy was given. The patient is alive and free of disease after 4 years but carries quite marked radiation effect.

Case 4. The patient was seen in 1957 with a full-term pregnancy. She had been under the care of an obstetrician in another country, where breast disturbance was noted and taken to be

inflammation of the breast and treated several weeks as such. Examination revealed "inflammatory carcinoma of the breast with metastases to the axillary and clavicular nodes and involvement of the chest and mediastinum." Biopsy under local anesthesia revealed widespread scirrhus of the breast. The baby was delivered in another city by cesarean section, and x-ray treatment was applied to the breast area. Death occurred approximately 3 months after conclusion of pregnancy.

Case 5. The breast lesion was discovered first by one of the student clerks in Maternity Out-Patient Department at near term. The patient refused to have biopsy during the course of pregnancy. During the puerperium, while the patient was in the hospital, biopsy was performed under local anesthesia and revealed the presence of scirrhous carcinoma. The patient accepted x-ray therapy but refused to have ultimate radical mastectomy; 4,600 r was given to the axilla, 4,320 r across the chest wall, and 4,500 r to the breast. The patient has been alive and apparently free of disease for 2 years.

Summary and conclusions

A report has been submitted of the cases of carcinoma of the breast in pregnancy which have been encountered during a survey of the breast carcinoma problem in Philadelphia. Observations have also been presented from the practice of an obstetrician and gynecologist who has been deeply interested in the problem of breast cancer detection and disposal.

On the basis of these statistics and studies the following conclusions are presented:

1. Breast disease in pregnancy is not uncommon and when it is overlooked or neglected the results are tragic.

2. Early and significant lesions of the breast can be detected in pregnancy only if the physician makes an irrevocable rule of including breast examination in each prenatal and postnatal visit of his patient.

3. Careful palpation of the breast will distinguish discrete masses from diffuse hypertrophy of pregnancy. There are no grounds for calling a discrete mass a "cyst" or a "milk duct."

4. "Inflammation" of the breast which

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does not subside or proceed to abscess formation after one week of therapy should be looked upon as possible inflammatory carcinoma.

5. Nodules of the breast which appear during the course of pregnancy are readily amenable to biopsy under local anesthesia without disturbance of the mother or the fetus. Biopsy is recommended in this situation as a separate preliminary procedure.

6. If the histologic diagnosis of cancer is established, thoughtful consultation must be devoted to the problems of disposal of the pregnancy and definitive therapy.

7. In view of the extremely serious nature of this condition, the rapid growth and metastasis that occur with the increased circulation of the breast, and the stimulus

of pregnancy hormones, I favor prompt termination of the pregnancy with or without ablation of the ovaries, preliminary x-ray therapy, and radical mastectomy where the situation is amenable.

8. It is probable that early diagnosis and effective prompt therapy may achieve results equivalent to those in nonpregnant patients of the same age.

I wish to express my appreciation to Dr. George P. Rosemond, Chairman, for the privilege of drawing upon the statistics of the Committee for the Study of Breast of Philadelphia, and to Irene Eldridge, Secretary, for making the desired histories available. I am also indebted to Dr. Paul L. Lewis of the Department of Pathology of the Jefferson Medical College for his review of pathologic material and help with the preparation of microphotographs.

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Discussion

Question. In a younger woman of childbearing age, who has had cancer of the breast with no metastasis, what is your advice about future pregnancy?

Dr. Montgomery. I would discourage future pregnancy. Future pregnancies may occur in spite of discouragement, and if they do occur and if the patient has no metastasis, I think the pregnancy must be carried to term.

Question. A 34-year-old wofnan with carcinoma of the breast and one axillary node that was positive 6 years previously, became pregnant again. What would be your management?

DR. Montgomery. I would sit down with the husband and wife and explain to them that the presence of pregnancy may be a very important factor in lighting up cells which at the moment may be inhibited or embedded and relatively inactive, and that the best policy from the standpoint of the disease itself would be interruption of the pregnancy.

Then I would let the decision rest with them as to what they wish to do. If they wish to follow the plan which seems safest as regards the breast disease, I believe under these circumstances interruption of pregnancy should be advised. If they wish to take a chance of acceleration of the disease and possible earlier return, then I think the decision must be theirs to make.

Question. You mentioned abdominal hysterotomy with possible hysterectomy. What would be the objection to abdominal hysterotomy and bilateral removal of the ovaries, without the hysterectomy in addition?

DR. Montgomery. I really can't see much advantage in leaving the uterus in if the ovaries are removed. It is my feeling that if one is going

to remove the ovaries one might as well remove the uterus also. The uterus does not appear to serve any purpose after removal of the ovaries, and it constitutes one of the areas in which trouble might occur in the future.

Question. When would you consider doing a mastectomy, preserving the pregnancy?

Dr. Montgomery. Under circumstances when the patient has personal reasons, religious and ethical, for avoiding the interruption of the pregnancy, a mastectomy during the course of pregnancy is the only recourse.

Very careful attention must be given to anesthesia, because the prolonged operation in a carefully performed mastectomy requires between $2\frac{1}{2}$ and 4 hours. One must be very sure that the patient is free of hypoxia during that time.

Question. In a woman who has had carcinoma of the breast treated surgically the question arises of her not having future pregnancies. Should we accept the surgeon's advice to sterilize her, so she will not become pregnant?

DR. MONTGOMERY. I would be loath under those circumstances to do a tubal ligation and would prefer to instruct her very carefully in contraceptive measures. If the disease was rather widespread at the time of the original operation, prompt oophorectomy should be done.

In many of these young women who have an anaplastic type of growth, and particularly if there is evidence of involvement of the axillary glands, I think a prompt bilateral oophorectomy is best under those circumstances.

DR. J. MILTON SINGLETON, Kansas City, Missouri. I have assumed obligation for careful breast examination of every patient who comes to my office. This routine was inaugurated by the loss of a patient one year after I had done the third and final successful operation on her for an extensive vesicovaginal fistula. While she was in the hospital she discovered a mass in her breast, and we called for a consultation. The surgeon said he felt it should be watched, but within a year the girl was dead of cancer of the breast.

I have tried to teach all patients self-examination of the breast by giving them pamphlets to read themselves and to give to their friends, these pamphlets being provided by the Jackson County Cancer Society. The results have been splendid.

Even with our breast examinations we have to ask the patient to help. As she becomes familiar with the procedure, she can more quickly note changes than we can by examination at prenatal visits or on a semi-annual basis. I have become so enthusiastic about results which I have obtained by passing out these self-examination breast pamphlets that I have petitioned a number of editors over the country to publish in the press pictures on breast self-examination along with other means of early cancer detection. I feel that if all of us would go home from this meeting with the inspiration Dr. Montgomery has provided, and could persuade the editor of our favorite paper to publish such material we would greatly reduce the incidence of death from cancer of the breast.

DR. MONTGOMERY. I can certainly endorse everything you have said, and I would like to add that 2 or 3 of the earliest cancers of the breast that I have ever seen were called to my attention by patients who had been practicing self-examination of the breast.

Question. May I ask for some advice on the problem of the bloody discharge from the nipple without the presence of a palpable mass.

Dr. Montgomery. A bloody discharge from the nipple without a mass being present should be considered highly suggestive of intraductal carcinoma. Sometimes this bleeding can emanate from intraductal papillomas. It is always rather embarrassing not to be able to palpate these areas. Oftentimes, however, by carefully mapping out the breast and putting pressure on the various quadrants and watching the nipple discharge, one can determine pretty accurately where the trouble lies.

Second, one may get some help from a soft tissue x-ray of the breast, because intraductal papilloma of the breast often casts a calcareous shadow on the x-ray. If you will get the radiologist to do some work in this field, which has been developed to a pretty high degree, perhaps he will be able to help you locate the trouble.

Then, of course, the thing to do is to excise that area. One starts with the margin of the areola or of the nipple itself, and carries the incision for an inch or an inch and a half, exposing the duct system as well as the breast lobule. Very frequently, as you incise down you will see the bleeding areas in the ducts.

If this condition persists, probably it is best to do a simple mastectomy, because you are dealing with a potentially serious condition.

Question. Have you the impression that there are differences in the behavior of a breast cancer

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upon which a pregnancy is superimposed and a breast cancer developing during pregnancy?

Dr. Montgomery. I suspect that the cancers we actually discover in pregnancy were present before pregnancy.

Question. I would like to know what your attitude is toward aspiration of an apparently cystic mass.

DR. MONTGOMERY. We do not practice aspiration of a newly found mass in the breast. We prefer to do a definite biopsy of the lesion, for several reasons. Often times cancer will lurk in the capsule of such a cyst. Likewise, we do not know the exact relationship between cysts of the breast and cancer.

In a woman who has extensive recurrent cystic disease, we oftentimes practice aspiration of the recurrent cysts after having done a primary biopsy perhaps a year or two earlier. Perhaps we are taking a little chance in so doing, but in some of these patients one would be doing biopsies of the breast every year, because these cysts reappear.

Question. Do you have any statistical evidence that interruption of pregnancy increases the longevity of a woman with cancer of the breast?

DR. Montgomery. No, I haven't and don't know of any sound evidence. I can only say that when we have a young patient who has had a metastasis the surgeons are very anxious for us to do a bilateral oophorectomy to arrest the effect of hormones upon the growth factor of the breast lesion.

If we perform a bilateral oophorectomy to arrest the effect of hormones upon metastatic disease or postmetastatic disease, it seems to me only rational to believe that the sooner we stop the 10 times or 100 times more active hormones of pregnancy, the more effective is going to be our ultimate therapy of the breast lesion itself or of the breast carcinoma.

Pregnancy in the adolescent girl

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PREGNANCY in the adolescent girl has apparently occurred with increasing frequency during recent years. The majority of modern authors agree that pregnancy and delivery in the adolescent are reasonably safe from the obstetrical point of view, provided that the patient has received what we think of as adequate prenatal care. However, most of the studies from this country 1, 2, 4, 5, 7-10, 12, 13, 15-18 and from abroad^{3, 6, 11}, 14, 19, 20 reveal that, except for the patients in various institutions such as the Salvation Army, Catholic, and other charitable institutions providing care and shelter for the unwed mother, most of the patients do not get adequate prenatal care and, even when they do, they present certain special problems in relation to prolonged labor, toxemia of pregnancy, and prematurity.

Clinical material

This study is confined to the obstetric patient of 16 years of age and under who received care at Metropolitan General Hospital and University Hospitals of Cleveland. These hospitals differ primarily in the fact that the former cares only for staff patients, whereas in the latter about 60 per cent of the patients are private. To simplify this presentation, our paper will be divided into

two parts. The first comprises those pregnancies terminating in abortion from the years of 1953 to 1959, inclusive; the second comprises those pregnancies which terminated with delivery of a baby weighing more than 500 grams during the years 1953 to 1959, inclusive, at Metropolitan General Hospital and in the years 1955 to 1959, inclusive, at University Hospitals.

Part I—incidence of adolescent pregnancies terminating in abortion

There were 2,332 staff patients who aborted, among whom 51 or 2.1 per cent were in this age group. In the same period of time, there were 1,511 private patients who aborted, none of whom were in this age group. The age distribution and the incidence of abortion is shown in Table I.

Sixteen of the 51 patients who aborted had had either a previous abortion or a full-term delivery prior to this aborted pregnancy. Approximately one third of these patients had evidence of sepsis on admission to the hospital.

There were 338 patients who had ectopic pregnancies of whom 3 or 0.8 per cent were in this age group. We have no further obstetric histories on these 3 patients.

Part II—incidence of adolescent pregnancy

The combined staff services had 1,080 patients of 16 years and under in 29,726 obstetric patients, an incidence of 3.63 per cent. There were also 3 patients, or an incidence of 0.02 per cent, in this age group, among 13,056 private patients.

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Presented at the Twenty-eighth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Kansas City, Missouri, Oct. 6-8, 1960.

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The distribution and incidence of adolescent pregnant patients per year is shown in Table II. Even though there was a steady increase in the total number of patients being delivered, the annual percentage of these patients has remained between 3.2 and 4.5 per cent.

The age distribution and incidence of pregnancies in adolescents is shown in Table III and, as might be expected, 60 per cent were in the 16-year-old group with a decreasing percentage in each year of age below 16.

Race. Negro patients numbered slightly over 90 per cent, and white patients made up the remaining 10 per cent in the study group. However, in the combined staff services of both hospitals, the ratio was about 80 per cent Negro to 20 per cent white patients (Table IV).

Marital status. We found that 60 per cent of the Negro patients were unmarried, whereas 65 per cent of the white patients were married (Table V). The higher incidence of mothers, separated in the latter group, suggests the possibility that some degree of parental authority induced marriages more frequently in the white girls. Marriage was very rare in girls of both races under the age of 15 years.

Gravidity. Slightly over 80 per cent of the patients were pregnant for the first time (Table VI), and approximately 20 per cent were pregnant for the second or third time. The 215 patients who had been pregnant more than once had had a total of 235 previous pregnancies, 23 of which had terminated in abortion.

Prenatal care. The stage of gestation in which these patients were first seen for obstetric care is illustrated in Table VII. It should be noted that only 5.8 per cent of these patients came during the first trimester and 150 patients or 18.9 per cent were not seen until they came into the hospital in labor. There were 355 or 58.5 per cent of our patients who had 5 or fewer prenatal visits, indicating inadequate or poor prenatal care. There were 205 or 33.6 per cent who had 6 or 9 prenatal visits and hence were

Table I. Age distribution of abortions and incidence

Age	Cases	%
12	1	2.0
13	1	2.0
14	11	21.5
15	14	27.4
16	24	47.0

Table II. Distribution and years incidence

Year	Patients	%
1953	104	4.5
1954	103	3.4
1955	151	3.2
1956	165	3.5
1957	197	4.0
1958	163	3.2
1959	200	4.0

Table III. Age distribution and incidence

Age	Patients	%
12	1	0.09
13	19	1.7
14	99	9.1
15	312	28.8
16	652	60.3

Table IV. Relation of age and race

Age	Negro	White
12	1	
13	17	2
14	92	5
15	284	28
16	582	72
Total	976 (90.2%)	107 (9.8%)

Table V. Marital status by race (per cent)

•	Negro	White
Single	60.6	29.9
Married	38.4	65.4
Separated	1.0	4.7

Table VI. Gravidity

Gravidity	Patients	%
i	868	80.1
ii	195	18.0
iii	20	1.8

Table VII. Stage of gestation when patient was first seen at CMGH

	No. Patients	%
First trimester	47	5.8
Second trimester	354	41.8
Third trimester	275	33.0
Labor	150	18.9

exposed to fair to good prenatal care. Only 48 or 7.8 per cent had the 10 or more visits necessary for excellent care.

Labor and delivery.

Duration of labor. The average duration of labor in the study group was 12.10 hours, which is approximately the same as that of 215 consecutive primiparous patients, whose average duration of labor was 11.30 hours. There was, however, an incidence of 7.8 per cent of patients with labor prolonged over 24 hours as compared to 4.6 per cent in the control group. We also found that these prolonged labors occurred most frequently in the patient 15 years of age and under.

Method of delivery. The methods of delivery were similar in the two institutions and are illustrated in Table VIII, which shows that 21.4 per cent of these deliveries were spontaneous. Delivery was by low and elective forceps in 61.8 per cent and by midforceps in 10.9 per cent including the forceps rotation from the posterior position by the Bill maneuver. We should also like to call attention to the fact that while the cesarean section rate was 2 per cent, the primary section rate was 1.8 per cent compared with at 1.4 per cent primary section rate at Cleveland Metropolitan General Hospital.

Twelve of 22 patients undergoing cesarean section had the operation performed for cephalopelvic disproportion. In all 12 of these patients, a test of labor and x-ray cephalopelvimetry was done prior to the cesarean operation. Cesarean section was performed in 4 patients with abruptio placentae and in 2 patients with toxemia of pregnancy. Out of the 1,083 patients, only 1 cesarean section was done for placenta

previa and 1 for uterine dyskinesia, by which we mean incoordinate and nonproductive uterine contractions. There were 2 patients with repeat cesarean section by the age of 16 years.

Maternal complications.

Toxemia. There were 109 patients, an incidence of 10 per cent, with toxemia of pregnancy. The large majority, 92 patients, had mild pre-eclampsia and 17 patients had severe pre-eclampsia or eclampsia.

In the group with severe toxemia, 14 of the 17 patients had received poor or no prenatal care.

The incidence of toxemia of pregnancy was markedly increased in patients 13 and 14 years of age, as compared to that in the 15- and 16-year-old patients (Table X).

There was also an increase in the incidence of severe pre-eclampsia and eclampsia in the 12- to 15-year-old age group as compared to the 16-year-old patients as shown in Table XI. This table illustrates that 13 or 3 per cent of the 12- to 15-year-old age group had severe pre-eclampsia or eclampsia

Table VIII. Method of delivery

Spontaneous	21.	4%
Low forceps	61.	8%
Midforceps	10.	9%
Breech	3.	8%
Cesarean section	2	0%

Table IX. Indication for cesarean section

Cephalopelvic disproportion	12
Abruptio placentae	4
Toxemia of pregnancy	2
Placenta previa	1
Uterine dyskinesia	1
Repeat cesarean section	2
Total	22

Table X. Incidence of toxemia of pregnancy according to age

Age	Cases	Incidence (%)
13	3	15.7
14	21	21.2
15	27	8.9
16	58	8.8

Table XI. Incidence of severe pre-eclampsia and eclampsia according to age

Age	Cases	Incidence (%)
12-15	13	3.0
16	4	0.6

Table XII. Relation of anemia to prenatal care

No care	20.1%
5 or less visits	13.3%
6 to 9 visits	11.8%
10 or more visits	10.6%
Incidence	15.6%

Table XIII. Hemorrhagic complications

Rupture of marginal sinus	2	
Premature separation of the placenta	5	
Abruptio placentae	5	
Placenta previa	1	
Postpartum hemorrhage	7	
Hypofibrinogenemia	2	

as compared to 4 or 0.6 per cent in the 16-year-old age group. We also found that there was a relationship between prenatal visits and toxemia of pregnancy. In the 355 patients with 5 or fewer visits there were 50 patients or 14 per cent with toxemia as compared to that of 253 patients with 6 or more visits in which we found 28 patients or 11 per cent with toxemia.

Anemia. We consider anemia to be present when the hemoglobin level is below 10 Gm. or the hematocrit determination less than 30 per cent. At delivery we found the hemoglobin level in 20.1 per cent of the no care patients was less than 10 Gm. (Table XII). There is a definite correlation between the hemoglobin level and the number of prenatal visits. The total incidence of anemia was 15.6 per cent.

Hemorrhagic complication. This complication occurred in 20 patients, of whom 10 had either premature separations or abruptio placentae. Two of the patients with abruptio placentae developed hypofibrinogenemia and required fibrinogin and blood transfusions. Postpartum hemorrhage (over 500 c.c.) was

present in 7 patients or 0.6 per cent (Table XIII).

Other complications. Positive serologic findings were present in 1 per cent of the study group as compared with 3 per cent of the remaining entire service. There were 6 patients with sickle cell anemia. Endometritis occurred in 78 instances, or 7 per cent of the postpartum patients. Urinary infection occurred in 25 patients, or 2 per cent. There were no maternal deaths.

The average weight of the Negro babies was 2,883 grams, whereas the average weight of the white babies was 2,979 grams. The total average was 2,892 which is 30 grams less than the average weight of the babies born of 1,000 consecutive primiparous patients used as a control group.

The adolescent patients were delivered of 4 per cent more premature babies, by weight, than the control group taken from 4,000 consecutive deliveries as shown in Table XIV. The stillbirth loss was similar in the two groups, but the neonatal deaths and perinatal mortality were slightly increased in the study group. This slight increase, we believe, is directly related to the increase

Table XIV. Prematurity and perinatal mortality (per cent)

	Study	CMGH
Prematurity	18.7	14.7
Stillbirths	1.9	2.1
Neonatal deaths	3.1	2.5
Perinatal mortality	5.0	4.6

Table XV. Malformations in babies

An	encephaly	2
	drocephalus	1
Me	eningocele	1
Dia	aphragmatic hernia	1
Ta	lipes	5
Ur	nbilical hernia	5
In	guinal hernia	5
	lydactyly	3
	descended testes	2
Hy	rdrocele	1
	lorospasm	1
	ngenital heart disease*	3
To	tal cases	29

*Diagnosis was made on physical examination and had no hospital follow-ups.

1937-1954 675 14-18

> 0.74 15:17 -0.58

4.43 -0.15

Table XVI. Differences and similarities found in the various studies

	Harris	Olsen	Posner and Pulver	Fairfield	Bromberg and Brzezinski	Nokes and Thornton	Seland
Years of study	Pre-	1910-	1923-	1931-	1929-	1936-	1934-
,	1922	1935	1933	1938	1940	1951	1953
No. of patients	500	269	100	74	136	894	397
Age of patients	12-16	13-16	12-15	13-15	14-16	13-17	14-17
Per cent negroes	68	_	_		-	45	-
Adequate prenatal care	-	-	-	91.9	-	31	-
Per cent toxemina	5.4	-	-	12.1	-	20.8	23.5
Per cent eclampsia	3.2	-	-	1.3	1.4	2.4	1.9
Length of labor (hours)	16	-		-	11:54	16:00	16:50
Per cent prolonged labor	-	_	_	-	-	-	27.7
Per cent cesarean section	2.2	-	_	1.3	_	2	0.5
Per cent postpartum hemor- rhage	-	-	-	-	-	1.5	33.4
Babies' weight (grams)	3,004	3,180	-	-	_	3,070	-
Per cent prematurity	-	_	17	-	-	-	10.4
Per cent perinatal loss	-		15.54	6.7	5.9	4.4	8.0
Incidence congenital defects	-	-	_	5.4	_	-	-
Per cent syphilis	5.2	-	8.6	-	_	2.9	1.5

of prematurity in the study group (Table XIV).

There were 29 instances of malformations, of which only 4 could be considered as incompatible with life. There were also 3 cases of congenital heart disease (Table XV). This diagnosis was made on physical examination and these babies had no hospital follow-up.

Comment and review of the literature

Harris in 1922 published the first paper in modern medical literature in regard to pregnancy in the adolescent girl. Since then we have found 20 papers which have appeared in foreign and American medical journals. A few of these papers have been concerned with comparison studies of the young and the elderly primipara.

We have attempted to assemble in a comparison table certain pertinent facts selected from 18 of these reports (including our own study) in order to show the differences and similarities found in the various studies (Table XVI).

The number of patients studied by the authors varied from 23 to 1,083. Whether the patient was white or Negro apparently meant very little, except that the white baby

weighed more on the average than the Negro baby. Premature delivery and toxemia of pregnancy occurred more frequently in the patients who received prenatal care, if any, on an outpatient basis compared to those who were in institutions, probably because diet, exercise, and weight could be more readily controlled in the latter group. Furthermore, there was a definite increase in obstetric and perinatal problems present in the patient who received poor or no prenatal care.

Fear, anxiety, and unhappiness may be factors in increasing uterine dyskinesia, and these aid, therefore, in causing the increased incidence of prolonged labor observed in these patients compared with that in the mature patients.

Toxemia of pregnancy varied in the literature from 5 to 21 per cent, with the majority of authors giving a ratio between 8 and 12 per cent. Eclampsia occurred in between 0.18 and 2.5 per cent of the patients reported.

Premature labor and delivery were present in between 10 and 18.7 per cent of the patients studied, and this we think is shown to be related directly to the prenatal care the patient had received.

and 34-53 7

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Moggian	Marchett and Menaker	Schmitz and Towne	Hacker	Arnold and Nelson	Morrison	Sinclair	Hofmeister and Burges	Poliakoff	Clough	Aznar and Bennett
1937-	1945-	Pre-	1949-	Pre-	1940-	1940-	1944-	1949-	1953-	1953-
1954	1947	1946	1951	1950	1950	1950	1953	1953	1956	1959
675	634	200	490	23	577	700	136	299	175	1,083
14-18	12-16	12-17	16	17	11-15	12-16	12-15	12-15	13-16	12-16
-	99	-	89	-	_	-	4.4	72.2	55	90
-	95	100	20	-	_	81.5	-	47.1	40	41.4
-	19.7	5.0	8.5	4.3	21.0	16.1	10.2	17.7	16.0	10
0.74	1.1	1.0	0.2	_	1.0	2.7	-	0.6	-	0.18
15:17	13:30	-	12:45	17:30		12:17	11:10	-	9:42	12:10
(min	6.3	9	8.1	19.6	9.6	4.3	6.6	4.4	_	7.8
0.58	0.6	0.5	1.6	8.7	3.6	1.3		1.0	2.3	2.0
-	2.0	4	-	-	1.7	0.5	8.1		2.9	2.0
_	3.147	-	nine .	3,289	-	-	-	-	_	2.892
Lean	14.8		17	_	16		_	17.4	****	18.7
4.43	3.8	4.5	-	mate .	3.8	-	4.4	5.9	_	5.0
-0	_	ente.	_	0.9	-	-	-	-	_	2.6
0.15	7.6	_	3.6	400	-	9.4	-	5.0	-	1

Perinatal loss varied from 3.8 to 15.8 per cent with the greater number of the authors showing the fetal loss to be between 4 and 6 per cent of the babies delivered.

The incidence of primary cesarean sections done for these patients was between 0.5 and 8.7 per cent, but the majority of the authors reported a cesarean section ratio between slightly under 1 per cent and slightly over 2 per cent.

Postpartum hemorrhages usually occurred in between 1 and 3 per cent of the patients reported, but one author had an incidence of 8.7 per cent in 490 deliveries and another reported an incidence of 33.4 per cent in 397 patients delivered.

Perinatal loss varied from a low of 3.8 per cent to a high of 15.8 per cent, but usually was between 4 and 7 per cent.

Summary

We have presented the results of a study of pregnancy in 1,137 adolescent patients of 16 years of age and under and have presented a review of the recent literature.

These patients presented an increase in the incidence of severe toxemia, especially in the girls of 15 years of age and under. There was also a higher percentage of prolonged labors as compared to that in a control group of primiparous patients. An increase in frequency of premature labor seemed directly related to an increased perinatal loss.

There was no apparent increase or decrease in the incidence of abortion. Fetal abnormalities and postpartum complications, compared to those found in the rest of the obstetric patients, were slightly increased. There was only a slight increase in the primary cesarean section rate. This was related to the slightly greater number of these patients who had either cephalopelvic disproportion or severe toxemia of pregnancy.

Conclusions

Pregnancy and delivery of the adolescent girl is reasonably safe, even though there is an increase in the risks to mother and child. However, no one believes it is desirable from a psychological, socioeconomic, maternal, fetal, or obstetric viewpoint.

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Discussion

Dr. Eva F. Dodge, Little Rock, Arkansas. Several years ago we decided to analyze 3,000 pregnancies in primiparas to see the effect of age upon primiparity. We found around 200 girls under age 17, the youngest at that time being 12 years old. Since then we have delivered two younger girls, 9½ years old and 11 years old, respectively. We think the 9½ year old girl probably holds the record for the United States. These girls had 3 to 12 months of menstrual cycles before they became pregnant. One of them had had many exposures before she became pregnant, according to her own statement. The other had not.

In the young primiparas there was a high

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incidence of prolonged labor and a very low incidence of cesarean section, but in the elderly primiparas there was a high incidence of cesarean section and a low incidence of prolonged labor. We tend not to have the courage to let them go to term. There was about the same incidence of toxemia and eclampsia in the younger group as in the group up to about 25 years of age.

Dr. Bennett (Closing). Dr. Aznar, who was with us at City Hospital for 5 years, was from Mexico City and returned there to practice, so was unable to be here to present the paper. He was responsible for collecting a great deal of the material before we put it together.

Uterosacral block and the obstetrical anesthesia problem

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IN SPITE of recent advances in analgesic and anesthetic methods, obstetricians are aware of the fact that labor and delivery continues to be an unpleasant experience for many of their patients. There remains a need for a safe and effective anesthetic for labor and delivery which may be widely used.

The problem

In the past we have looked to the anesthesiologists to help us solve our problem. However, if we analyze recent trends, it is apparent that they alone will not provide the solution. The need for anesthesiologists would be met only if all the graduates from all the medical schools in the country for the next 10 years became anesthesiology residents.8 It is likely, therefore, that the rate of increase in births in the next 10 years will exceed the rate of increase in the number of anesthesiologists available for 24 hour obstetrical coverage. This will result in a relative decrease in the number of anesthetists engaged in obstetrical anesthesia. Therefore, the responsibility for adequate obstetrical anesthesia must be accepted by obstetricians. Women should be encouraged to demand adequate, effective, and safe anesthesia. They should be taught to expect labor and delivery to be a pleasant experience. Since there is no one anesthetic method ideal for all patients, obstetricians should be familiar with different techniques so that they can fit the anesthetic to the patient rather than the patient to the anesthetic.

Uterosacral block as a useful tool for the solution of the problem. In March, 1959, after learning of the work by Spanos and Steele,7 we began to use uterosacral blocks for pain relief in labor and delivery. The first report in the American medical literature on the use of pericervical anesthesia in obstetrics was by Rosenfeld⁶ in 1945. Freeman⁴ described a method using a No. 17 needle as a guide for injection and found 2 per cent lidocaine hydrochloride with epinephrine as the drug of choice. Recently, Mengert and Slate⁵ have reported on the use of pericervical anesthesia as a satisfactory anesthetic for outpatient diagnostic dilatation and curettage.

As demonstrated by anatomic studies by Campbell² and recent clinical studies by Doyle³ and others, the sensory nerve supply of the cervix and most of the fundus pass laterally via the pelvic plexus in the area of the sacrouterine ligament and base of the broad ligament. These are mostly sympathetic nerves which pass to the level of the lower thoracic cord. Other sensory pathways via the ovarian plexus (sympathetic) and nervi erigentes (parasympathetic) do not

From the Department of Obstetrics and Gynecology, St. Mary's Hospital. Presented at the Twenty-eighth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Kansas City, Missouri, Oct. 6-8, 1960. appear to play an important part in the total picture of pain relief in childbirth. The relationship of the parasympathetic and sympathetic nerves to the motor function of the uterus is not so clearly understood. The variable motor effects noted with various regional anesthetics seem to indicate that these are related to multiple factors: the cord level, as in spinal and caudal analgesia; whether or not labor is well established; and the ability of the patient to use the auxiliary muscles of labor.

At any rate, uterosacral block does interrupt the pain impulses from the fundus, cervix, and upper vagina. There are several advantages to this type of procedure. First, it is a simple technique and easy to teach or to learn. Second, it is a safe procedure free from the danger of massive intradural or intravenous injection. No hypotension has been observed as with spinal or caudal analgesia-and there is no problem of postpartum headache. As with all regional anesthetics, the mother is awake and participates in the delivery. In our study we were alert to the possible disadvantage of depression of fetal heart rate and even fetal death. However, our results will show that our fears in this regard were unfounded.

The study

St. Mary's is a 320 bed hospital with 54 bassinets. There are an average of 3,100 deliveries annually. This report deals with a detailed study of 108 of our earlier cases. These blocks were done by the house staff, general staff, other specialists, and the authors. Fifty-five per cent were done by specialists and 45 per cent were done by house staff and general staff.

Technique. Usually transvaginal pudendal block was done to eliminate perineal sensation. With the same 6 inch, 20 gauge needle and a 10 c.c. Luer-Lok syringe, and with the forefinger used as a guide, 10 c.c. of the anesthetic agent was injected submucosally high in the vaginal fornix at 4 and 8 o'clock so that a palpable wheal was felt. This technique, described first by Spanos and Steele, differs from previously reported paracervical

blocks in two important particulars. First, the needle is inserted at 4 and 8 o'clock instead of at 3 and 9 o'clock. However, we have found that the site of injection need not be as accurate as in other nerve-blocking techniques. When the baby's head was low in the pelvis, we occasionally injected as high up on the lateral vaginal wall as possible and found that we still got good pain relief. This probably indicates that the nerve fibers, which we block, are diffuse, running in a network through the base of the broad ligament

Table I. Premedication

	No.		
Dosage	patient		
Secobarbital	1		
100 mg.	55		
200 mg.	1		
	56		
Meperidine and promethazine			
75/25	30		
50/25	35		
100/25	10		
None	9		
Other	24		
	108		

Table II. Character of contractions at onset of the block

Quality	
Mild	5
Strong	103
	108
Frequency	
5 minutes or more	10
5 minutes or less	98
	108

Table III. Agents used for the block

per cent hexylcaine		
10/10		66
15/15		12
Other		3
		81
per cent lidocaine		
10/10	f	19
20/20	,	7
5/5	,	1
		27

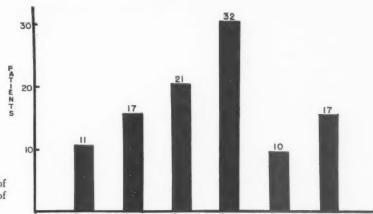


Fig. 1. Dilatation of cervix at the onset of uterosacral block.

and not limited to the sacrouterine ligaments. The anesthetic agent reaches the nerves by rapid diffusion through the tissues. Second, the injection is made just beneath the mucosa rather than deeper in the paracervical tissues. This is important because we feel that it avoids the risk of intravascular and intraperitoneal injection associated with deeper insertion of the needle. This increases the safety for both mother and fetus.

Since patients in labor have most discomfort at the end of the first stage and just before delivery, we tried to initiate the block as a terminal procedure no longer than one hour prior to expected delivery. Reinjection was necessary in 7 patients. Premedication was administered as required (Table I). Usually, secobarbital was given on admission and some combination of meperidine and promethazine later if necessary. We have found, in making the transition to complete regional anesthesia, that, except for a barbiturate, premedication can be omitted in most cases. Actually if doses of analgesics were not kept low, after administration of the block the patient was disofiented and uncooperative and many of the advantages of this technique were lost. In most instances, we felt that contractions should be strong and frequent before the block was instituted Table II). As in other forms of regional block, we found some evidence that contractions would slow if injection was too early. The cervix was dilated 8 cm, or more in most patients (Fig. 1). Generally, in primiparas we waited for the cervix to dilate more than in multiparas before starting the block.

Because of the previously reported advantages of 1 per cent hexylcaine (hydrochloride), we used this agent in 75 per cent of our cases. Since we had been using 1 per cent lidocaine for pudendal blocks, it was used in the remaining 25 per cent (Table III). We usually used 20 to 30 c.c. of hexylcaine and not over 40 c.c. of lidocaine. In these early cases, we used nitrous oxide previous to block in 36 cases out of 108. As we became more familiar with the technique, we found that this was seldom necessary. We learned not to call the anesthetist unless the block was inadequate for delivery.

Results. We used the same classification of results as Spanos and Steele:

Excellent. The patient had no sensation of contractions, no supplemental anesthesia was required, and in most instances she had to be told when to bear down.

Good. The patient was aware of mild suprapubic pain or backache, but still needed no supplemental anesthesia.

Fair. The patient experienced definite pain relief but supplemental anesthesia was required.

Poor. There was no apparent pain relief from the block.

The results are summarized in Table IV. For the last year we have averaged about

50 uterosacral blocks a month at our hospital. We have more confidence in the blocks, and therefore have 85 to 90 per cent excellent and good results.

The effect of the block was prompt. In a few instances we observed unilateral pain relief during injection. The duration of the block was defined as the time from injection to delivery or reinjection. As seen in Table V, most of our patients were delivered within 45 minutes after injection. This does not mean that the anesthesia lasted only that long. We know that it lasted longer in several instances since we were able to explore the fundus manually or with instruments post partum with no additional anesthesia. We did not observe any significant difference in the duration of effect between lidocaine or hexylcaine.

We have the definite clinical impression that this short time from block to delivery was caused by an acceleration of labor. The cervix impressed us as becoming flaccidly paralyzed. No matter what dilatation was present when blocking was carried out, progression to "complete" was usually accomplished by a few contractions.

There were 67 normal spontaneous deliveries (62 per cent). Low or outlet forceps were used in 33 patients (30 per cent of our series). This was almost twice our over-all forceps incidence (Table VI). With a combination of uterosacral and intravaginal pudendal block, the head rapidly came down to the perineum. However, the involuntary "bearing-down reflex" was absent. Although the abdominal muscles were not affected and the patients were coached as to when to bear down, many of them could not effect delivery promptly. Therefore, low or outlet forceps were used to accomplish easy delivery.

Table IV. Uterosacral nerve block results

Duration of block	No. of patients
15 minutes or less	23
15 to 45 minutes	69
45 to 90 minutes	16

Table V. Uterosacral nerve block

Type of delivery	
Spontaneous	67
Outlet forceps	17
Low forceps	16
Scanzoni rotation	2
Breech	3
Twins	. 2
Triplets	1

Table VI. Uterosacral nerve block results

Pain relief	No. of patients		
Excellent Good	45 37 }78%		
Fair Poor	${21 \atop 5}$ ${22\%}$		

Complications. There was one definite maternal complication. This was a generalized clonic convulsion lasting for approximately one minute. Following it delivery continued uneventfully and there were no postpartum sequelae. It was felt that this occurred as a result of rapid intravascular absorption of 1 per cent hexylcaine from the pudendal site. Following this case we restricted the use of hexylcaine to uterosacral block only and used 1 per cent lidocaine for pudendal block. There were two other maternal convulsions observed in our series. It is questionable, however, that they occurred as a result of the injection of an anesthetic agent since they occurred in an epileptic and a pre-eclamptic patient. In both instances the subsequent intra- and postpartum course was uneventful for both mother and baby.

There were no fetal complications attributable to the anesthesia. There were no stillbirths and only one neonatal death in our series of 108 cases. The baby that died was a 7 month, premature infant weighing 4 pounds, 8 ounces. He appeared to be in good condition at birth and required no resuscitation. However, he died 18 hours later of atelectasis. We do not feel that the anesthesia in any way contributed to this death. We have actually been impressed by

the rapid cry and good color of these babies upon delivery.

Comment

We observed rapid progress to delivery following blocking. This we feel is due to specific blocking of the motor nerves to the cervix. Generally, there was no effect noted in the regularity or strength of fundal contractions. In a few instances, when the block was probably started too soon, we did observe some slowing of progress due to a decrease in frequency and intensity of contractions. This phenomenon is also noted in other regional anesthetic techniques and is consistent with neurohumoral aspects of the mechanism of labor recently described.¹

Some patients with good relief of pain will feel mild discomfort in the suprapubic area, groins, or sacrum. We suggest that this may be due to failure to block certain somatic nerves such as the ilioinguinal and iliohypogastric nerves which arise from the upper lumbar and lower thoracic cord. Nerves which pass through the ovarian ligament also were not blocked.

As with all types of regional anesthesia, we observed some patients who were not good

candidates for uterosacral nerve block because of fear and anxiety of childbirth and regional anesthesia in general. We did not withhold general inhalation anesthesia in these cases. Most patients, however, were delighted to be awake and to witness as well as to participate in their delivery. Even those patients who expressed doubts as to their desire or ability to stay awake were thankful for the experience afterward.

Summary

- 1. A detailed analysis of 108 uterosacral nerve blocks for pain relief in labor and delivery is presented.
- 2. Seventy-eight per cent of our patients had excellent and good results. Except for pudendal block, no other anesthesia was required for delivery.
- 3. There were no adverse fetal effects resulting from this technique of nerve block.
- 4. One definite maternal complication was observed. This generalized clonic convulsion was probably due to intravenous absorption of 1 per cent hexylcaine from the site of pudendal block. There was no serious sequela.

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Discussion

DR. JAMES G. MULE, New Orfeans, Louisiana. The role of the professed anesthesiologist should not be minimized since there are certain patients and complications of pregnancy which demand his expert attention. Since these problems are often unforeseen, the obstetrician is more secure with the constant availability of one who is well oriented in the practice of all types of obstetric anesthesia for any condition. In those areas where the group practice of anesthesiology can

provide it, 24 hour physician anesthesia service seems to be the best approach to this problem.

In addition to the advantages of the local infiltration anesthesia outlined by Dr. Aldridge, it is essential to stress the advantage of uterosacral block for the patient in premature labor where ordinary dosages of analgesia are contraindicated. On the other hand, some of the disadvantages of this method are identical to those of other types of regional anesthesia. The authors

state that this block should not be performed too early in labor because it will decrease the quantity and quality of uterine contractions. I would like to have this point more clearly defined by centimeters dilatation of the cervix. The authors recommend initiation of the uterosacral block approximately one hour prior to delivery because of the relatively short duration of the anesthetic agents and the difficulty in administration when the presenting part is well descended into the pelvis.

The latter is also true for the transvaginal pudendal block which was developed on the LSU Division of Obstetrics and Gynecology in Charity Hospital of New Orleans in 1954. However, the number of transvaginal blocks is dependent upon the level of training of the house staff coupled with the allotted time for individual patient care. It becomes obvious that the latter factors are influenced in turn by the pace of the delivery service. When the presenting part has descended to the level of the perineal floor the transperineal approach is preferred.

Although the technique is simple enough, the procedures for administration could be time-consuming and expensive. In many hospitals the labor area is inconveniently removed from the delivery suite. Limited nursing help and the demand for two or more trips of the patient to the delivery room do promote a disturbance in already overburdened hospital routines. Although these objections are not of paramount importance, they should be considered in the over-all evaluation of new procedures.

We cannot draw any conclusions about the toxicity of the agents employed in this series of patients, but it is essential to emphasize the dangers involved with local infiltration as with other forms of regional anesthesia. Convulsion in 3 of 108 study patients is probably out of proportion to those in the over-all obstetrical population in this hospital. Although these complications could be coincidental, the authors justly emphasize the importance of barbituate premedication and proper dosages of drugs for infiltration anesthesia.

Dr. D. W. Freeman, Minneapolis, Minnesota. The technique Dr. Aldridge has described is similar to paracervical blocks, as he indicated. That injections into the parametrium diffuse widely throughout the pelvic connective tissues has been demonstrated. Sedoff injected radiopaque material by the paracervical block tech-

nique and demonstrated by x-ray that this spreads widely throughout the extraperitoneal connective tissue and the base of the broad ligaments.

The technique described as paracervical block was used originally in France and was used first in this country by Rosenfeld around 1945. We have been interested in it for a number of years, and some years ago we published results on approximately 500 such blocks. Since then we have done many more. Our results have been good.

We use a technique that is similar. We inject from 5 to 10 c.c. into the parametrium. We also add to it at about 4 and 8 o'clock. We found, when we analyzed our results, that they were just as good with 5 or 6 c.c. as with 10 c.c.

The injection is facilitated by the use of a guide such as was first described by Dr. John Gillam, who is now at Fargo. He conceived the idea of using a needle which carried up into the lateral fornix first. The needle is long enough so that it projects beyond the introitus, and then the needle through which the injection is made is threaded through this. This method makes it much easier to reach the area when the baby's head is well down in the pelvis. It also limits the depth of the injection. The needles are selected for length so that the injection can be made approximately $1\frac{1}{2}$ cm. into the parametrium.

The blocks can be done any time in the first stage of labor and can be repeated if necessary. Actually, the procedure is theoretically applicable to all patients, but it is limited by practical considerations. A physician must be there to do it for he cannot ask the nurse to do it for him. We do it in the delivery room under sterile conditions—and a delivery room is not always available.

We find the blocks are applicable in about two thirds of our patients at the present time. In the multiparas we do them when the cervix is dilated perhaps 4 to 6 cm., and in primigravidas 6 to 7 cm. We also do transvaginal pudendal blocks at the same time.

We have had about a 10 per cent failure rate, which we are unable to explain. It does not have to do with spread of the anesthetic. Our results were no better when we added a spreading agent such as hyaluronidase. Indeed, results were better when we used epimephrine in the solution, which one would think offhand would limit the spread of the agent and result in even more failures.

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or ir iThe present drug of choice (and we have used about all of them) is mepivacaine. In 100 mepivacaine blocks we have done recently there have been only two failures. Mepivacaine is more stable than the other local anesthetics, and perhaps this is the reason for its being more effective. We have not found the blocks have any effect on labor except to speed it up occasionally by softening the cervix, as Dr. Aldridge has indicated.

Dr. Leonard R. Howard, Salina, Kansas. I would like to report on a series of 96 patients treated by me in the past year, during which time 163 patients were used as controls. The only essential difference in the two groups was the use of the uterosacral block.

I am primarily interested in uterosacral block as a second-stage anesthetic, since we have one nurse anesthetist serving our hospital on 24 hour call. The results in relief of pain are very similar to those described by Dr. Aldridge. According to the classification of Spanos and Steele, there were 37 per cent "A" results and 40 per cent "B" results, giving a 77 per cent satisfactory anesthesia versus 13 per cent "C" and 6 per cent "D," or 19 per cent unsatisfactory results.

The most striking difference in the two groups seems to be the absence of the bearing-down reflex, as described by Dr. Aldridge, in the non-uterosacral block control. Eighty-three per cent of the babies were delivered spontaneously, and 13 per cent by forceps. With uterosacral block 40 per cent were delivered spontaneously and 57 per cent were delivered by forceps. There were also 2 cases of manual removal of placenta, one occurring an hour and a half after delivery when one of my general medical officers called me in consultation. We gave the patient a uterosacral

block and removed the placenta, saving her the hardship of general anesthesia.

Dr. Aldridge (Closing). Dr. Mule mentioned the importance of the anesthesiologist, and I certainly agree with him. However, I believe we are all aware of the fact that there is a shortage of anesthesiologists, as far as obstetrics is concerned, in perhaps a majority of our hospitals around the country. Therefore, we do need something to use that will make it possible for us as obstetricians to give relief to our patients.

As regards the dilatation of the cervix, I believe I mentioned we did not pay too much attention to it because the character of the contractions seemed more important. A dilatation of 8 cm. or more was our average in the primipara. In the multipara we sometimes started these blocks when the cervix was dilated from 3 to 8 cm., and we found that artificially rupturing the membrane at the same time resulted in delivery within an hour after the block.

It is true that three convulsions in 108 patients is a high percentage, but in light of our experience since then we feel this is probably related to the agent. There have been others who have reported hexylcaine as being particularly likely to cause convulsions in paravertebral blocks, for instance. So, we feel that 1 per cent lidocaine is a very safe drug, and we hope to continue to use this for some time.

We have only one small misgiving about the use of mepivacaine. In perhaps 1 out of 12 cases we found that the fetal heart tones decreased to 85 following administration of a block of mepivacaine, which condition we did not find with any of the other agents. Although the baby was fine, with the fetal heart tones returning to normal after the 5-minute period, we do not want to take any chances of getting into trouble.

Blood secobarbital levels and their clinical correlation in mothers and newborn infants

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THE fact that newborn infants delivered of heavily sedated mothers often demonstrate respiratory depression at birth has been widely emphasized with the laudable intention of deterring physicians who practice obstetrics from the great temptation of providing maternal comfort by the use of large doses of analgesic drugs. Without wishing to detract from these sensible precautions, we have observed that many infants born of heavily sedated mothers do not show signs of depression at birth, and therefore have undertaken this study to determine whether any pharmacologic explanation of this "discrepancy" of effect on mother and infant can be found.

The general plan of the study was (a) to administer sodium secobarbital (Seconal), a short-acting barbiturate widely used in obstetrics, at various times before delivery, (b) to determine simultaneous maternal and cord blood secobarbital levels, (c) -to record the degree of sedation of the mother and infant at delivery, and (d) to compare when possible blood levels of the mother and her infant at varying times after birth.

From the Department of Anesthesia and the Division of Obstetrics and Gynecology, Mount Sinai Hospital, and the Cuyahoga County Coroner's Office.

This investigation was supported by grants from Eli Lilly and Company.

Presented at the Twenty-eighth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Kansas City, Missouri, Oct. 6-8, 1960.

Method

Within a 1 to 2 minute interval 200 to 300 mg. sodium secobarbital was given intravenously to mothers from 1 minute to 337 minutes prior to delivery. Patients selected were considered to be at term and were delivered vaginally or by elective cesarean section, usually under spinal anesthesia. Parturients with recognized complications which might of themselves lead to infant distress were excluded from the study. When necessary, patients received additional medication, usually consisting of minimal doses of meperidine and scopolamine. Maternal venous blood samples were drawn immediately before the injection of sodium secobarbital, and again as close to the actual time of delivery as possible. Cord blood samples were obtained by gravity or by stripping from the placental end of the cord.

In the first and major part of the study whole blood analyses were performed on oxalated blood. Later, part of the oxalated blood was centrifuged for separation of the plasma from the cells, and each portion was then analyzed so that whole blood and plasma levels could be compared. A third subordinate study compared the ability of maternal and infant plasma protein to bind secobarbital. Analyses were conducted by a semi-micro modification of Goldbaum's ultraviolet spectrophotometric method for barbiturate determination.1 The optical density difference curve was used to characterize secobarbital as opposed to its metabolites, other barbiturates, or artefacts.

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In calculation of secobarbital levels the maternal control reading (the blank) was subtracted from both the maternal and cord blood readings. Since we have no evidence that the maternal blank was necessarily applicable to cord blood, some possibility of error exists in those cases where the blank reading was appreciable (equivalent to 2 mg. or more per liter).

Method of evaluation of mothers and infants

Since the respiratory center of the newborn at birth is unusually sensitive, not only to drugs but to the anoxia and trauma of delivery, and since the mother's respiratory center is not grossly affected by the profound sedation produced in this study, a comparison of the respiratory center depression of mother and infant would have neither purpose nor value. We therefore classified the mothers on the basis of depth of sedation using the five grades as described below:

Grade I. Minimal sedation—awake, but sleepy; rational.

Grade II. Mild sedation—asleep but easily roused by voice or pain; answers questions rationally.

Grade III. Moderate sedation—deeply asleep, can be roused with difficulty, and when roused is mentally sluggish or irrational.

Grade IV. Deep sedation—comatose, cannot be awakened but responds to pain; lash reflex and jaw muscle tone present.

Grade V. Very deep sedation—comatose, no lash reflex or jaw muscle tone; little or no response to pain; vital signs unchanged.

In regard to the infant we have made the assumption that an infant which required resuscitation but was then indistinguishable in vital signs from the unsedated infant can hardly be considered to have an equivalence of hypnotic effects as its unresponsive and unconscious mother. Apgar² has discussed some of the difficulties of evaluation of newborn infants. Her scoring system has been used as a basis for the following classification of depression in newborn infants.

Grade I. All infants with scores of 8 or more at one minute after birth.

Grade II. Initial score under 8, but scoring 8 or more after simple resuscitation, and within 5 minutes after birth.

Grade III. Not reaching a score of 8 within 5 minutes, but condition satisfactory (>8) within 15 minutes.

Grade IV. Has not reached a score of 8 within 15 minutes after birth.

Results

A. Clinical effects on mother and baby. Complete blood level studies were performed on 51 mothers and their infants. In 25 additional maternal-infant pairs, only clinical evaluation of depth of sedation was performed. Table I summarizes the sedative effects noted in these 76 mothers and infants and shows that 44 of the 76 infants studied were in Grade I and needed no resuscitative measures. Twenty-four additional newborn infants were in Grade II. Of the 6 classified as Grade III, 5 were exposed to additional factors of (a) more than minimal narcotic medication, (b) general anesthesia, or (c) difficult delivery; conditions which of themselves might have caused or increased depression. One of the 2 severely depressed (Grade IV) infants was anoxic because of cord compression; the other was exposed to narcotic medication and a drop in maternal blood pressure associated with spinal anesthesia. In short, 90 per cent of infants studied (68 of 76) showed little or no obvious depression. Of the 8 which were grossly depressed, 7 had been exposed to

Table I. Correlation of maternal sedation with grade of infant

Grade of	Grade of infant						
mother	I	II	III	IV	Total		
V	13	9	5	1	28		
IV	20	6	1	1*	28		
III	6	6	-	-	12		
II	3	1	_	-	4		
I	2	2	-	-	4		
Total	44	24	6	2	76		

*Cord compression—three times around neck.

Table II. Correlation of grade of infant with time of birth after administration of secobarbital

Secobarbital injection	Grade of infant			
(minutes)	I	II	III	IV
1- 5	14	4	1	0
6- 10	7	5	1	1
11- 15	3	2	1	0
16- 25	9	4	3	0
26- 35	3	2	0	0
36- 45	4	1	0	0
46-337	4	6	0	1*
Total	44	24	6	2

^{*}Antenatal anoxia.

Table III. Correlation of cord blood levels with grade of infant

Amount of secobarbital per liter		Gra	de of in	nfant	
(mg.)	I	II	III	IV	Total
0-1.9	8	5	1	0	14
2.0-3.9	13	8	0	1	22
4.0 - 5.9	9	5	2	0	16
6.0-7.9	2	1	0	0	3
8.0 - 9.9	1	0	0	0	1
Total	33	19	3	1	56

additional factors which might have caused depression.

Further analysis of the correlation of depth of infant depression with grade of maternal sedation reveals that the incidence of grossly depressed infants (Grades III and IV) was 21 per cent (6 of 28) in Grade V mothers, 7 per cent (2 of 28) in Grade IV mothers, and zero (0 of 20) in Grade I, II, and III mothers. Statistical analysis of these data by the chi square method reveals that the difference between the first group (infants born of 28 Grade V mothers) and the other groups combined is just significant at the 5 per cent level, and this does not take into account the fact that factors other than secobarbital may have played a part in some of these cases of depression in infants.

Even if we accept that there is an increased incidence of depression of infants born to the most heavily sedated mothers,

the salient fact is that most infants (79 per cent) born to such mothers are not grossly depressed.

Table II reveals no marked correlation of the condition of the newborn child with the time after secobarbital administration. It can be noted that, excepting the one caused by cord compression, all major cases of depression (Grades III and IV) occurred in infants born within 25 minutes of the administration of intravenous sodium secobarbital. Statistical evaluation of the significance of this difference is not attempted because of the small numbers involved and the presence of other variables which might have affected the results.

Table III shows the lack of correlation between the cord blood level of secobarbital and the degree of infant depression.

No serious maternal complications occurred in this series. However, it is important to report that 3 mothers retched and vomited while under heavy sedation. Although clinical aspiration did not occur, vomiting and aspiration are potential hazards of sedation profound enough to diminish or delete protective reflexes. It need hardly be stated that such levels are not only undesirable but also unnecessary for adequate production of amnesia in the mother.

B. Secobarbital levels in maternal and cord blood at delivery. In 21 control cases, bloods were drawn from mothers who had received no barbiturates prior to delivery. Secobarbital determinations were performed, and these controls were read as having 0 to 3.35 mg. secobarbital per liter of whole blood. The average reading was 0.45 mg. per liter and all but 3 were 0.85 mg. per liter or less. High controls were distinguished from low barbiturate levels by analysis of ultraviolet spectrophotometric sorption data as previously described. Cord blood samples drawn 1 to 337 minutes after the intravenous administration of sodium secobarbital to 51 mothers had whole blood levels ranging from 0 to 9.7 mg. per liter. Synchronous maternal whole blood levels ranged from 0 to 23.9 mg. per liter.

The ratios between cord and maternal

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blood levels were determined and related to the time of administration. It was noted that in the first two minutes (5 cases) the cord-maternal ratio was under 35 per cent in 4, although virtual equilibration occurred in one pair at 1½ minutes after administration. Of the 47 specimens drawn 3 or more minutes after drug administration, the ratios were distributed as follows: 28 between 50 and 91 per cent, 6 over 100 per cent, one too low for comparative reading, and the remaining 11 ranging from 9 to 46 per cent. The average ratio in bloods drawn over 3 minutes after drug injection was 71 per cent.

Fig. 1 is a scattergram which reveals not only the marked variation in secobarbital levels in the 51 mothers studied, but also the general trend of these levels in relation to time. The superimposed diagrammatic curve indicates this general trend. From an initial injected dose of approximately 50 mg. per liter (calculated on an average blood volume of 5 L. and an instantaneous intravenous injection of 250 mg. sodium secobarbital) there is a rapid drop in blood levels to 10 mg. or less within 3 minutes in

most of the cases, and 5 mg. or less within 7 minutes.

On this same figure is placed the scattergram of the cord blood levels of secobarbital, with the superimposed diagrammatic curve representing the trend of blood levels in relation to time. This curve shows a rise during the first 2 to 3 minutes, then declines slowly parallel with but below the maternal curve.

Fig. 2 demonstrates the apparent lack of correlation of the depth of maternal sedation with the whole blood secobarbital level. As compared with the rapid drop of secobarbital blood level immediately after administration, the initial peak hypnotic effect persisted for from 20 to 60 minutes and decreased while the blood level remained relatively unchanged. Within the first 20 minutes of sodium secobarbital administration, 46 of 47 mothers were classified in Grade IV or Grade V. In the next 20 minute period, 10 of 14 mothers were so classed.

C. Comparison of plasma and whole blood levels. Whole blood and plasma secobarbital levels were compared in some

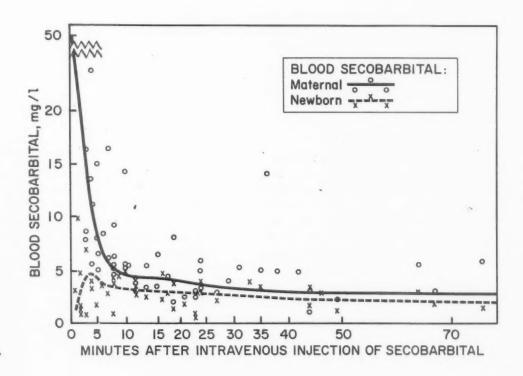


Fig. 1.

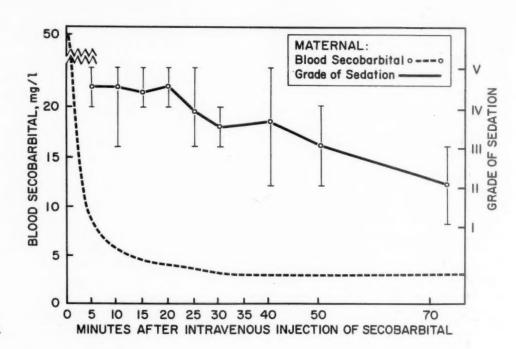


Fig. 2.

mothers and infants. Secobarbital appeared to be present in greater concentration in plasma than in red cells, for most plasma levels were higher than the corresponding whole blood levels. This relationship was not a consistent one, for the ratio between maternal plasma and whole blood levels varied from 0.73 to 2.0, with an average of 1.28. The cord blood ratios varied from 0.85 to 1.53, with an average of 1.17. There was no consistent relationship between the ratios obtained for mothers and their respective infants.

D. Postpartum studies. Table -IV compares secobarbital blood levels of 11 mothers and infants at delivery with the levels at 42 minutes to 9 hours post partum. It is noted that the healthy full-term infant represented in this study is apparently capable of readily eliminating secobarbital from his blood stream. In fact, it appears that the infant's blood level declines faster than the mother's.

Comment

Evaluation of the cause of depression in the newborn is always complicated by the multiplicity of possible etiological factors. Aside from the obvious anoxia due to such causes as known placental separation, prolapse or knotting of the cord, or the evident obstetrical trauma of a difficult breech or forceps delivery, it is always possible that milder degrees of anoxia or trauma occur during labor and delivery and are not recognized. Hon3 has concluded from his studies of fetal electrocardiograms that frequent and strong contractions may produce significant intrauterine anoxia, and Maxwell4 has suggested that occult prolapse of the cord may be more common than usually believed. Hence, it is not possible in any given case to state dogmatically that medication is solely responsible for an observed depression.

The results reported in this study, as well as in a number of clinical and laboratory studies with thiobarbiturate anesthesia for delivery⁵⁻⁸ indicate, not an absence of any depressant effect on the infant, but remarkably little over-all effect considering the relatively profound hypnotic state of the mother. Depth of maternal sedation, time of secobarbital administration, and cord blood level of secobarbital have all been shown in this study to be poorly correlated with the degree of depression in the infant.

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If blood level of secobarbital is closely correlated with its effect as is known to be the case with inhalation anesthetic agents such as ether or cyclopropane, then differences between the effect on mother and infant would have to be due to differences in blood levels of the drug to which each is exposed.

Previous studies⁶⁻⁹ indicate that the short-acting and ultra short-acting barbiturates rapidly traverse the placenta and reach and maintain a state of virtual equilibration between the mother and infant thereafter. This study, too, demonstrates similar findings.

Although the results we have reported show wide variation and a few bizarre readings, these can be well explained by (1) the relative difficulty of the analytic technique used and the possibility of certain technical errors and (2) the small concentrations of these drugs in blood even with the larger than usual clinical dosages used.

Is there a possible explanation for the average cord-maternal blood ratio of approximately 70 per cent obtained in this study? One possible source of error in our study was the use of whole blood rather than plasma determinations. However, analysis of the data in which whole blood and plasma levels are compared reveals that these differences were not of great significance in affecting our results. The known difference in hematocrit determinations on mothers

and newborn infants was taken into consideration in this analysis.

The phenomenon of protein binding of barbiturates¹⁰ might account for differences in plasma concentration of secobarbital in maternal and cord blood, if differences could be demonstrated between protein binding of mother and infant. However, we performed studies in which known quantities of secobarbital were added to paired samples of maternal and cord blood and then dialyzed. No significant differences in protein binding of mother and infant were revealed.

Another possible explanation of this moderate discrepancy between maternal and cord blood levels is that the cord blood we used is not the villus lake blood which actually is the pool exposed to substances in maternal blood.

Whatever explanation is found for this difference, on purely theoretical grounds it does not seem conceivable that substances capable of traversing the placenta as rapidly as do the barbiturates would not achieve complete equilibration between the maternal and fetal blood exposed to each other in the placenta. Moreover, even if a small difference were present in the blood level to which mother and infant were exposed, this could hardly explain the marked difference of effect usually seen clinically.

We must assume, therefore, that blood level of secobarbital is not closely correlated

Table IV. Data on comparative secobarbital levels at delivery and post partum in mother and infant

Secobarbita	al levels of infants (m	g. per liter)	Secobarbital	levels of mothers (n	ng. per liter)
At birth	Post partum	Minutes post partum	At delivery	Post partum	Minutes post partum
4.1	1.9	42	7.9	4.4	67
2.0	0.8*	60	2.9	not done	
8.0	1.0	66	11.4	not done	-
5.3	3.3*	72	14.3	7.0	52
4.8	1.8*	88	6.5	1.1*	83
2.6	0	88	3.1	0.6	113
3.7	2.1*	110	8.0	4.2	100
4.7	0	155	2.7	1.9	170
5.9	1.2	7 hrs.	4.9	2.2	6 hrs
3.5†	5.7*	8.5 hrs.	5.3	1.4*	9 hrs
2.2	0	9 hrs.	8.0	0	9 hrs

^{*}Negative for barbiturate, probably a metabolite.

[†]Only slightly positive for barbiturate.

with the state of depression at a given time. Fig. 2 shows this poor correlation. Whereas almost all mothers remained heavily sedated for 20 to 60 minutes after the administration of secobarbital, the blood level dropped sharply in the first few minutes and then remained practically unchanged during the period of decrease in maternal effect.

We wish to present a hypothesis to explain both the lack of correlation of maternal effect with blood level and the relative freedom of the infant from a depression comparable to that observed in the mother after administration of secobarbital and related drugs intravenously.

We postulate that the maternal peak effect is related to the initial peak cerebral arterial concentration to which the brain is exposed and to some degree to the duration of exposure. Since the initial blood concentration immediately after injection must be in the range of 50 mg. per liter and since this level drops rapidly to under 10 mg. per liter, the speed of such drop being presumably greater than the speed of placental transmission, the fetal brain can never be exposed under these circumstances to a peak concentration more than 20 per cent as great as the peak maternal concentration.

If this hypothesis is correct, certain tentative conclusions might be drawn.

1. Intravenous anesthesia with barbiturates will probably spare the fetus more than inhalation anesthesia to a comparable depth. Since effect of inhalation anesthetics is closely correlated with their blood levels, once equilibration occurs the infant would be expected to be approximately as deeply anesthetized as the mother at the time of delivery. However, clinical exceptions to this are often noted. Protection against fetal depression may be afforded by (a) anesthesia as light as possible, (b) delivery before equilibration occurs, and (c) the use of inhalation agents shown to be least depressant to the newborn. With intravenous anesthesia, speedy delivery is no protection as it has been shown that thiopental sodium rapidly crosses the placenta and reaches peak concentration in the infant within 1 to

2 minutes. We do not feel that this can be used as an unqualified endorsement of thiobarbiturates as the ideal general anesthesia for obstetrics. The maternal risk must be taken into account. It may be that maternal vomiting would be associated with a higher incidence of dangerous laryngospasm under intravenous thiobarbiturate anesthesia than under any of the various inhalation anesthetics.

2. Intravenous medication during labor may have certain advantages over other routes. If a given level of hypnosis is to be obtained it will require a considerably smaller dose intravenously to produce the same effect as a larger dose orally or intramuscularly. Not only will the desired effect be obtained more rapidly, but also the eventual blood level, after sufficient time for distribution throughout the body, ought to be lower.

We believe we have provided a sufficient explanation for the relative lack of depression in infants born of mothers profoundly sedated by intravenous secobarbital in the behavior of maternal blood levels after administration. However, a theoretical analysis of the fetal circulation brings out other factors capable of modifying the effect of drugs crossing the placenta. Price11 has shown that the distribution of thiopental in the body after intravenous injection can be explained on the basis of differential blood flow. Organs like the brain and liver rapidly achieve high concentrations of the drug not because of any tissue avidity but because of the high blood flow to these organs which assures that they will be exposed first to the initially high concentrations of drug in the blood stream.

The circulation of the fetus has several factors reducing the concentration of barbiturate before it reaches the cerebral arteries. Reynolds¹² has shown that blood entering the fetus from the placenta often passes through the liver. Until the liver cells attain a concentration of barbiturate equal to that in the blood entering the liver, most of the barbiturate reaching this organ will remain in it. This may account for the de-

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lay in reaching a peak cerebral artery concentration.

A second factor is the considerable dilution of barbiturate-laden umbilical vein blood by the vena cava before this blood reaches cerebral arteries. Another factor is the likelihood that cerebral blood flow is proportionately much less in the fetus than in the adult. These three factors combine to decrease and delay the exposure of the infant brain to drugs entering the fetal circulation.

Summary

- 1. Seventy-six mothers received 200 to 300 mg. secobarbital intravenously at varying times before delivery. All mothers and infants were classified according to degree of depression noted at delivery. In 51 mothers and infants simultaneous blood secobarbital levels were determined at birth.
- 2. Seventy-nine per cent of infants born to the group of mothers under the heaviest sedation (Grade V) were not grossly depressed.

- 3. Secobarbital rapidly crossed the placenta with virtual equilibration between maternal venous and newborn cord blood within 3 minutes.
- 4. The maternal blood secobarbital concentration dropped at least 80 per cent within 3 minutes.
- 5. The fetus was rarely exposed to more than 20 per cent as much as the initial maternal secobarbital level.
- 6. This difference in peak secobarbital concentration may account for the clinical differences noted in mothers and infants. Fetal circulation contains other mechanisms which may further decrease the exposure of the fetal brain to depressant drugs.
- 7. Seven of the 8 depressed babies were born within 25 minutes of secobarbital administration. Their cord blood secobarbital concentration showed no correlation with the degree of depression.
- 8. Postpartum studies of secobarbital blood levels indicated that full-term infants eliminated secobarbital from their blood streams as readily as did their mothers.

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Discussion

DR. GEORGE W. MORLEY, Ann Arbor, Michigan. Fetal depression as a result of barbiturate administration to mothers in the first two stages of labor has long been thought to have a direct cause-and-effect relationship. This impression may have arisen from its use with inhalation anesthetic agents as well as in its association with other factors causing fetal depression.

The authors have confirmed the work of others in regard to the poor correlation between secobarbital blood levels in mothers and infants and the sedative level of the offspring. In view of this variability, more emphasis should be placed on the clinical observations of the patients and their infants when this drug is administered. In addition, the authors have shown a marked differential between maternal sedation and fetal depression in this study. This differential still exists even though secobarbital is of low molecular weight and traverses the placental and blood-brain barrier by simple diffusion.

According to Table I in this study, the authors found that 68 of the 76 infants delivered were

classified Grade I and II. Twenty-four of these 68 infants (approximately 33 per cent) were in Grade II and required simple resuscitation—a term which deserves further definition and clarification. A comparative study using the Apgar scoring system applied to infants born of patients who had no sedation would be important. I don't believe the number of infants delivered under regional block analgesia alone requiring simple resuscitation would be this high. Apgar reports an 8.9 average score in 692 patients delivered under spinal anesthesia and 9.1 average score in 102 patients delivered under caudal analgesia without supplemental medication.

It is also important to remember that whereas the pharmacological levels of barbiturates 4 hours after birth may have no effect on the respiratory center of the infant, the same level at birth may have a significant inhibitory effect on the initiation of respirations. A great physiologic effort is required to initiate this act.

The results of this work suggest a wider margin of safety for secobarbital administration in obstetrics than has been previously recognized. If conduction anesthesia is not available or if sedation is required for other reasons, the drug should be administered by the route of choice in adequate dosages but early in labor. Its greatest effect is in combination with meperidine, meperidine-promethazine mixtures, or with other similar phenothiazine or piperazine derivatives. When used alone, larger doses of secobarbital are required since it only obtunds pain by impairing consciousness.

I would like to ask Dr. Root two questions: (1) You pointed out the advantages of intravenous administration of secobarbital—are these advantages significant enough to encourage this route of administration in preference to the more popular oral and intramuscular routes? (2) Do you favor the general use of phenothiazine and piperazine derivatives as premedicants in obstetrics and gynecology?

Dr. Root (Closing). We must point out that we were primarily interested in the pharmacologic dynamics and an explanation of the events that occur. In no way do we imply that 250 mg. of secobarbital is a safe and recommended method of analgesia in labor.

The term "simple resuscitation," should perhaps be explained. This means one of two methods—either taking an infant who is a little flaccid, spanking him on the soles of his feet to stimulate a good cry and deeper breathing, or taking the resuscitator and providing a few breaths of positive-pressure oxygen.

The point we did make about this was not that these infants did not show any respiratory center depression at birth, but within a few minutes they did not look drugged, and therefore we could not see how one could say that the initial depression was due to any drug depression comparable to that seen in the mother. We feel that if there were ways of measuring the respiratory center depression of infants, drugs of this sort could be shown to decrease the ability of that respiratory center to respond at birth.

As far as using secobarbital alone is concerned, we do not use it that way in our hospital. For a number of years we have been using almost entirely intravenous medications at Mount Sinai Hospital in Cleveland. The usual routine followed by those obstetricians who require reasonably heavy, that is, amnesic medication consists of 100 mg. of Demerol, ½50 mg. of scopolamine, and 100 mg. of secobarbital given together. These are not given in the same syringe because the secobarbital and the other two drugs are incompatible. A rather high degree of amnesic effect can be obtained from this routine.

We have not been impressed by the toxic effects of such medication, although in some quarters this is considered fairly heavy. We have recently initiated studies for a blind comparison of this medication with a combination containing 50 mg. of promethazine or promazine, and 50 mg. of meperidine with ½50 mg. of scopolamine. The medications given are not known to the observer, and careful evaluations are made.

We are attempting to determine maternal differences. We do not think that in a series of just a few hundred cases one can really tell the difference—whether infants are going to be better with one kind of medication or another. We think the factors affecting infants are far more related to obstetrical and other considerations than to well-given medications.

Whether to use promethazine in addition to or in place of secobarbital is something we are trying to determine. The advantage of promethazine is that it allows reduction in the dose of meperidine, yet provides an equivalent analgesic effect and an equal hypnotic effect.

The disadvantage so far is the possibility of blood pressure changes associated with the use of this and similar drugs, and we have seen some that might be of some hazard to the mother We have seen both hypertension and hypotension

Abdominal exploration

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ROUTINE addominal exploration should be practiced by all gynecologists doing intraabdominal operations. A review of the literature shows scant reference to this very rewarding procedure. Abdominal surgery is not felt to be complete without evaluation of all the significant areas and organs.

A routine for this examination is necessary to avoid missing some region. The order of approach leads one first to the site with the lesions for which the surgical procedure was undertaken. After evaluation of this, one should next proceed with the general examination. The routine should belong to the individual gynecologist and completeness will include the following areas: appendiceal area, small bowel, large bowel, liver, gall bladder, kidneys, adrenal gland areas, stomach, spleen, pancreas, great vessels, hernial sites, omentum, and bladder.

The exploration should usually be carried out as soon as the peritoneum is opened. When gently done, this does not adversely affect anesthesia. Occasionally, an unexpected finding may have to be given priority over the planned procedure or the unsuspected disease could influence the choice of operation.

Little time is required for a systematic exploration. Pratt¹ felt that most explorations could be accomplished in one or two minutes, and Colcock² stated that the procedure should require only a few minutes. In a part

of our own study the time for exploration was investigated. The time required in 257 operations in which abdominal exploration was carried out was compared with the time for 103 operations in which the procedure was omitted. Those in which exploration was done averaged 2 minutes more operating time. This method of arriving at the time required for exploration is, of course, not statistically meaningful, but it does indicate the insignificance of the time factor when this procedure is considered.

Exploration presents a chance to evaluate areas otherwise relatively inaccessible. Suspected conditions can be confirmed, unsuspected findings may suggest potential trouble. This knowledge can be utilized in prophylaxis and treatment. Expensive laboratory and x-ray procedures may be avoided. Future surgical requirements can be planned with greater consideration for safety and economy. The physician's confidence in future problems is bolstered by this examination. The difference between real and imagined ills may be partially differentiated by prior exploratory findings. With each succeeding case, exploration will prove its worth. Each of us remembers patients whose wellbeing has been enhanced by this examination. The reasons for exploration are numerous; there are a few valid reasons for not explor-

The most obvious contraindication to exploration is the presence of inflammation, including genital tuberculosis. Local anesthesia, of course, does not permit this procedure. The poor surgical risk patient and the patient in uncompensated shock are not usually explored. Even in these two instances,

From the Department of Obstetrics and Gynecology, the Holzer Hospital and Clinic.

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Table I. Results of abdominal exploration in 500 operations

Total explored	500	(100%)
Exploration positive	116	(23,2%)
Individual lesions noted		
Gall bladder disease or stones	74	
Kidney	15	
Meckel's diverticulum	7	
Colon	7	
Liver	3	
Myoma	3	
Metastatic disease	2	
Gastric ulcer	1	
Rib defect	1	
Pancreatic cysts	1	
Spleen adhesions	1	
Calcified nodes	1	

however, exploration can be considered, for some poor-risk patients tolerate the primary procedure much better than anticipated. The patient in shock may respond rapidly to corrected blood loss and removal of its source. These patients should be re-evaluated after the primary operation, and the opinions of both operators and the anesthetist are then assessed. If they are in agreement, exploration should be performed. This is the case with exploration following cesarean section. There may be other circumstances militating against exploration but without some very good reason, exploration should be done habitually.

Pratt¹ noted additional findings in about 47 per cent of the patients he explored. Some of these conditions were suspected and exploration was merely confirmatory. Many lesions noted had given no indication of their existence prior to exploration.

In the present study, involving 500 abdominal gynecological procedures, a significant finding during exploration was noted in 23.2 per cent. Adhesions were not recorded in this analysis, which may account for a lower percentage.

The frequency of the various positive findings is shown in Table I. The value of exploration must not be expressed by this alone. The 77 per cent with negative explorations should share in the value of this procedure, for these patients have the reasonable assurance that all else was clear.

Summary

1. The reasons for exploration are numerous; there are few valid reasons for not exploring. 2. Of the 500 cases reviewed, 23.2 per cent showed some significant finding.

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Malignant mixed Müllerian neoplasms (mixed mesodermal tumors)

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MALIGNANT mixed Müllerian neoplasms are much more frequent than is usually supposed. While individual case reports are still frequently seen, we agree with Morehead and Bowman that these tumors are not extremely rare.¹ Only meticulous examination of adequate biopsy and surgical specimens can reveal their actual number. It has not been unusual for an initial biopsy specimen to be diagnosed as carcinoma. The true nature of the tumor was discovered by reviewing questionable slides and obtaining adequate tissue for study.

In the literature these neoplasms have been described under a variety of names including mixed mesodermal tumors, sarcoma botryoides, and carcinosarcoma.²⁻⁴ The first two terms are unsatisfactory because they are nonspecific. The term "carci-

nosarcoma" conversely is too specific, and all tumors of this group cannot fulfill the criteria necessary to be so classified. Sternberg and collaborators⁵ reported an analysis of 21 of the above neoplasms that occurred at Charity Hospital from 1946 through 1952, emphasizing their malignant character and presenting evidence of their origin from endometrial, endocervical, and vaginal epithelial stroma. Further, they found that the carcinomatous elements were limited to those of the epithelia of the female genital tract, as the epithelia of the analagous Wilms tumors and malignant embryonal hepatomas are limited by the potentialities of their respective anlage.5 This is therefore a very particular and specific type of tumor. It is different from teratomas, in which there is no such limit on epithelial variety. The term "malignant mixed Müllerian neoplasm" was suggested. It is precise. It emphasizes the malignant character, the system of origin, and the limited differentiation of the epithelial elements characteristic of the lesion.5

Credit for the initial description of these neoplasms belongs to Weber⁶ for his case report in 1867. There have been many reports since then, most of which are limited to single cases with discussions of theories of origin. In addition there are several excellent reviews of the literature.^{4, 7-9}

From the Department of Obstetrics and Gynecology and the Department of Pathology, Tulane University School of Medicine and the Division of Obstetrics and Gynecology and the Division of Pathology, Tulane Unit, Charity Hospital of Louisiana.

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The theories of origin have classically been the cell rest theory of Cohnheim and that of metaplasia of a pluripotent tissue (Pfannenstiel). Sternberg and collaborators after a detailed examination of 21 cases supported the theory Pfannenstiel¹⁰ suggested in 1892. They feel that this neoplasm arises from the epithelial stroma of the endometrium, endocervix, and the upper vaginal epithelium of children. They point out that this tissue appears primitive and theorize that it has pluripotential capabilities. Although the epithelial components in tumors arising from this stroma are limited to those of the female genital system, this is not true of the sarcomatous elements. Their studies further showed that this tumor is often of multicentric origin and characteristically begins in the epithelial stroma and never deep within the organ. Carcinomatous as well as sarcomatous structures seem to develop without sharp transition from the primitive stromal background. It is our purpose to add to the previous series from this hospital and to present in detail the rather definite and ominous clinical aspects of this interesting neoplasm.

Material

By adding 30 cases to the previous study, we can now evaluate 51 instances of malig-

Table I. Incidence

	No.	%
Carcinoma of cervix	6,135	11.5
Carcinoma of endometrium Malignant mixed Müllerian	695	1.1
neoplasm	51	0.1

Table II. Age

Decade	No. cases
1st	2
2nd	1
3rd	0
4th	0
5th	7
6th	11
7th	24
8th	4
9th	1
10th	1



Fig. 1. Surgical specimen of a 57-year-old patient with malignant mixed Müllerian neoplasm of the uterus (Case 261007).

nant mixed Müllerian neoplasm from a single institution. All of the patients were from Charity Hospital at New Orleans and were seen between Jan. 1, 1946, and March 1, 1960. The following clinical picture of this entity was obtained from these cases.

Clinical picture

Incidence. In this series, malignant mixed Müllerian neoplasm occurred as 0.1 per cent of all gynecologic admissions. For every 14 endometrial carcinomas and for every 120 cervical carcinomas there was one malignant mixed Müllerian neoplasm. Of the last 30 cases 30 per cent were originally diagnosed as carcinoma at the initial biopsy. Only careful review of adequate material revealed the exact diagnosis (Table I).

Age. This is a neoplasm primarily of the menopausal and postmenopausal age groups. While ages varied from one to 96 years, almost half (48 per cent) occurred in the seventh decade and 22 per cent in the sixth decade. In addition, all but 3 cases occurred at age 40 or beyond.

The years of active childbearing seem remarkably free of this disease in our locality. In the remaining 3 cases, 2 patient were prepubertal and one was puberta (Table II). Age at menopause also seem to be of some importance in that 29 percent of these patients menstruated at age 50 or beyond.

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Parity. The number of conceptions seems to be of little importance. Among the postpubertal group there are almost the same number of grand-multiparous patients as those who did not conceive at all. However, there are fewer patients in the range that conceived 2 to 4 times. The total number of patients who had abortions was 17 and the total number of abortions for the group was 36 (Table III).

Previous irradiation. It is interesting to note that 2 patients had previous irradiation for carcinoma of the cervix 11 and 13 years before diagnosis of malignant mixed Müllerian tumor. These patients apparently developed, at age 63 and 69, respectively, a new malignancy after complete irradiation therapy. These, however, were the only 2 patients in the entire series that received roentgen therapy prior to the occurrence of malignant mixed Müllerian neoplasm.

Race. The ratio of white to Negro was

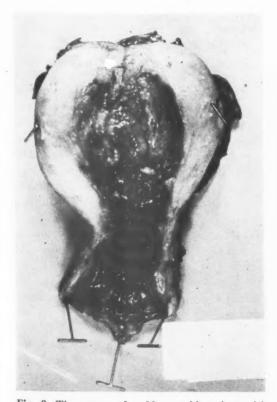


Fig. 2. The uterus of a 66-year-old patient with malignant mixed Müllerian neoplasm 125421).

Table III. Parity*

No.	Gravidity	Parity	No. of abortions
0	13	20	31
1	- 8	3	10
2	2	5	2
3	5	4	1
4	3	3	1
5	17	13	3

*The history on one patient contained no data on parity. Two prepubertal patients are omitted,

1 to 3. This frequency in Negroes is less striking than in previous publications. The ratio of white to Negro gynecological admissions is 1 to 2 and there may therefore be a higher incidence in the Negro race.

Location of original lesion. This malignancy is so rapid in its growth that by the time the patient is initially examined the exact area of its origin may be difficult to determine. By careful review one is, however, able in most instances to determine the site. In this series the tumor originated in the uterine corpus in 36 instances. In 11 additional cases the lesion was so advanced that one could ascertain only that it arose from either the uterus or the cervix. In one patient it arose in the cervix and in 2 from the posterior vaginal wall. In the remaining case the lesion began either in the vagina or cervix. This overwhelming occurrence of uterine lesions agrees with the findings in other published reports^{4, 5} (Table IV).

Gross appearance. The appearance of the tumor varied according to its cellular constituents and their degree of differentiation. There is a tendency toward polypous growth from multiple sites in the endometrium. As the growth fills the endometrial cavity it presents through the dilated cervix as a necrotic, infected mass with an altered appearance. In the uterus and deep to the necrosis it appears as an opaque, grayish white to reddish blue soft irregularly polypoid (grapelike) mass. These masses appear to begin in the endometrial and endocervical stroma.

At the time of the patients' appearance in the clinic 55 per cent of the lesions were visible with the bivalve speculum as either

Table IV. Location of lesion and age of patient

Site of lesion	No. cases	Age (years)
Vagina	2	1 and 5
Cervix	1	13
Cervix or vagina	1	69
Uterus or cervix	11	40-68
Uterus	36	40-96

Table V. Symptoms

Vaginal bleeding	45	
Vaginal discharge	14	
Abdominal pain	14	
Weight loss	12	
Tumor	5	
Anorexia	4	
Hematuria	2	
Ascites	2	
Dysuria	3	
Abdominal tenderness	2	
Urinary incontinence	1	
Passed tissue	1	
Nausea	1	
Vomiting	1	
Abdominal distention	1	
	Vaginal discharge Abdominal pain Weight loss Tumor Anorexia Hematuria Ascites Dysuria Abdominal tenderness Urinary incontinence Passed tissue Nausea Vomiting	Vaginal discharge 14 Abdominal pain 14 Weight loss 12 Tumor 5 Anorexia 4 Hematuria 2 Ascites 2 Dysuria 3 Abdominal tenderness 2 Urinary incontinence 1 Passed tissue 1 Nausea 1 Vomiting 1

Table VI. Survival

Years	No. living	
1	· 11	
2	1	
3	i	
4	0	

Table VII. Therapy

Modality	No.	Average survival (months)
Radium	2	8.7
X-ray	1	3
Radium and x-ray	12 ~	9.9
Radium and x-ray and nitro- gen mustards	1	8
Extensive operation	7	7
Extensive operation and x-ray	1	7
Extensive operation and x-ray and radium	12	13
Extensive operation and radio- active gold	1	24
Extensive operation and nitro- gen mustards	2	10.7
Extensive operation and thio- TEPA	1	5
Extensive operation and x-ray and radium and nitrogen		
mustards	1	24
None	10	1.6

cervical or uterine tumors presenting through the cervix.

Microscopic appearance. These tumors arise from the endometrial stroma from multicentric sites. The most frequent sarcomatous element, as one might expect, was endometrial sarcoma characterized by poorly differentiated cells with sparse cytoplasm, crowded nuclei, and indefinite cell borders. Often striated muscle and cartilage could be seen, surrounded by, and apparently originating from, nests of endometrial sarcoma. Rhabdomyosarcoma cells could be identified by the typical eosinophilic, granular cytoplasm with cross striations in some cells. Areas of leiomyosarcoma, fibrosarcoma, chondrosarcoma, and lymphosarcoma were also observed.

The carcinomatous portions of some of these tumors resemble the epithelium of the Fallopian tube and serous cystadenomas even to the occurrence of psammoma bodies. More frequently, however, endometrial carcinoma, papillary carcinoma, and mucinous carcinoma were seen. All were limited to epithelium of the Müllerian system.

Metastases. In the previous series from this institution as well as in the patients seen since then, distant metastases were the rule rather than the exception. In addition, it was found that either or both the sarcomatous and carcinomatous elements of the neoplasm may be involved in the distant or local extension. Of the entire series only 2 patients died without evidence of metastasis. The first died of cardiac disease during irradiation therapy, and the second of a pulmonary embolus on the eighth postoperative day after extensive hysterectomy and pelvic lymph node dissection.

There was early metastatic spread by direct extension to contiguous structures such as cervix and vagina and to a lesser extent the bladder and rectum. Distant lymphatic spread to all pelvic nodes, the preaortic nodes, and in three instances the mediastinal nodes was readily apparent. There was also hematogenous spread to all major abdominal and thoracic organs and in one patient to the lumbar vertabrae.

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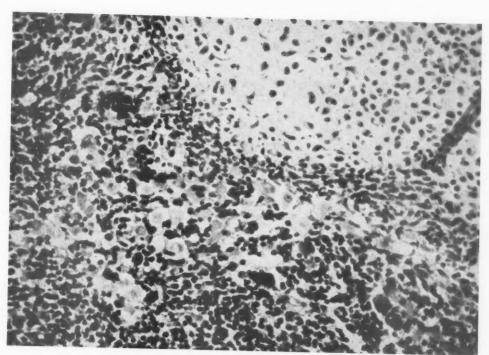


Fig. 3. Area of chondrosarcoma in endometrial sarcoma in a 59-year-old patient (Case 311018).



Fig. 4. Striped muscle cell in a malignant mixed Müllerian neoplasm of the uterus (Case 55317).

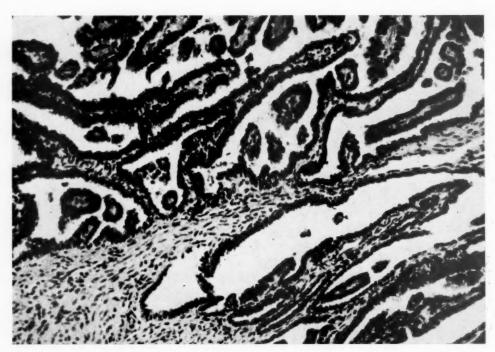


Fig. 5. Papillary adenocarcinoma resembling tubal carcinoma or serous cystadenocarcinoma (Case 317231).

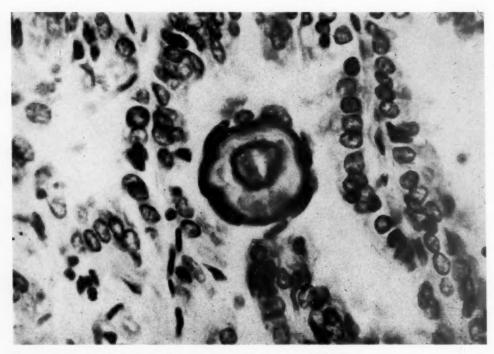


Fig. 6. Psammoma body in papillary adenocarcinoma (Case 317231).

Symptoms. The most common complaints of these patients were vaginal bleeding, lower abdominal pain, weight loss, and discharge. Bleeding was by far the single most frequent symptom and it varied from one week to 6 years in duration before the patient sought help. Bleeding presented either as a bloody discharge, intermenstrual spotting, postcoital spotting, hyper- and polymenorrhea, or postmenstrual bleeding. In addition there were 2 cases of hematuria.

Pain occurred in 14 instances and, as one might expect, it was usually lower abdominal pain. There were, in addition, 14 patients complaining of a discharge, which was purulent in 10 and watery in the remaining 4. Weight loss was the next most frequent symptom and it was present in 12 instances (Table V).

Prognosis. Malignant mixed Müllerian neoplasm is one of the most rapidly growing and fatal tumors encountered by the gynecologist. The "5 year cures" recorded in the literature are singularly sparse and, in this series of 51 patients there were none. Two patients are alive 6 months after therapy at present. Forty of our patients were dead in one year, and 49 had died after 2 years. Survivals varied from one day after diagnosis to 31/2 years. Two patients in this series died of causes other than the neoplasm, i.e., cardiac disease and pulmonary embolism. While the degree of malignancy varies from tumor to tumor, the prognosis of this neoplasm is particularly ominous (Table VI).

Treatment. Table VII lists the different types and combinations of therapy used in these patients with the average survival time. This variety of therapeutic measures has been used because no single method has proved to be outstanding. It is true that in many patients there was an overly long patient delay before medical care was sought, and in others the treatment was delayed by the difficulties encountered in obtaining a definite diagnosis.

Irradiation has been ineffective. Similarly,

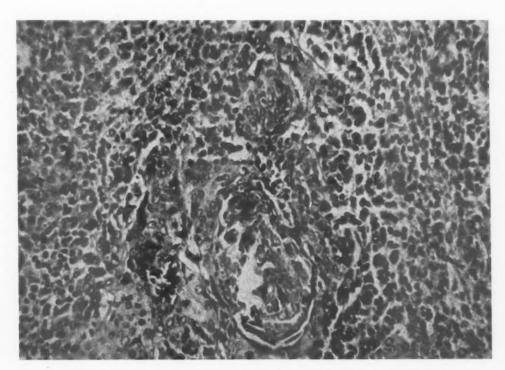


Fig. 7. Epidermoid carcinoma with central keratinization and poorly differentiated sarcoma (Case 40047).

nitrogen mustards and thio-TEPA as presently given are also ineffective. Surgery seems to offer more than all the other therapies employed and the operation should be done early and be sufficiently extensive to encompass the lesion. The minimal surgical procedure should be an extensive (Wertheim) hysterectomy and pelvic gland dissection with or without a vaginectomy. More often, however, an exenteration may be necessary because of early invasion of the bladder and/or rectum.

We are exploring the area of therapy by combining isolated pelvic perfusion¹¹ with extensive operation at the suggestion of Dr. Conrad Collins in the hope that our survival rate will be improved. By doing an isolated pelvic perfusion we will be able to perfuse higher concentrations of nitrogen mustards into the pelvis in an attempt to halt the progression of the neoplasm. This is to be followed by the definitive operation. With the advent of better chemotherapeutic agents this method of attack can only improve results. Time also is a most important factor and therapy must be begun as early as possible.

Comment

In order that all mixed Müllerian neoplasms may be diagnosed some diligence on the part of the clinician and the pathologist is required. In no other aspect of gynecological malignancy is adequate biopsy material more important. The incidence at our hospital is increasing with the persistence with which it is sought. This is a disease primarily of the menopausal and postmenopausal age groups, reaching its peak in the seventh decade. In addition, age at the menopause may be significant in that 29 per cent of the patients in this series menstruated after the age of 50. While the active childbearing ages were remarkably free of this disease there were two prepubertal and one pubertal case.

Malignant mixed Müllerian neoplasm appears to begin in the stroma of the endometrium and to a lesser extent in the stroma of the endocervix or that beneath the upper vaginal epithelium. It begins from multicentric foci as polypoid structures enlarging until they may present at the cervical os or even the introitus. At this time the tumor may resemble a leiomyoma or have the classic grapelike appearance that led to naming this entity "sarcoma botyroides." Histologically, the sarcomatous elements have unlimited differentiation, while the carcinomatous portions are limited to that epithelia normally occurring in the Müllerian system. Thus, this neoplasm is not a teratoma in which the carcinomatous elements would not be limited to one system.

All but 2 patients gave evidence of local and distant metastases and these metastases were either of the sarcomatous or carcinomatous elements whether they occurred in lymph nodes or other sites.

The most important symptoms were vaginal bleeding, vaginal discharge, lower abdominal pain, and weight loss in that order. In some instances symptoms were present as long as 6 years, representing patient delay. The most obvious physician delay was caused by the difficulty in obtaining an exact diagnosis. In over half of our cases, however, the diagnosis could be suspected on pelvic examination alone.

The prognosis in these tumors has been particularly fateful. The average survival has been 8.5 months from the time of diagnosis. In the 2 patients who are still living, the diagnosis was made less than 6 months ago.

With prognosis so guarded it is imperative that we offer these patients more than one usually associates with maximum treatment for malignancy. In addition, irradiation which one is prone to fall back upon has proved on the Tulane Service to be of little or no value. Early extensive operation, the minimum of which should be an extensive hysterectomy and pelvic node dissection, must remain the sheet anchor of therapy. We hope that by combining it with the isolated pelvic perfusion method developed by Tulane Department of Surgery we may perfuse increased concentrations of nitrogen mustards or other chemo-

therapeutic agents into the pelvis and increase the salvage rate.11

Summary

- 1. Fifty-one cases of malignant mixed Müllerian neoplasms are reviewed.
- 2. The clinical picture is reviewed in detail.
- 3. Methods of therapy with survival times are presented.
 - 4. Suggestions for therapy are made.

We wish to express our appreciation to the Department of Obstetrics and Gynecology of Louisiana State University for the use of their material and the Independent Obstetrics and Gynecology Service of Charity Hospital for their cooperation.

Discussion

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Dr. Clyde J. Geiger, Chicago, Illinois. This appears to be the greatest number of cases of mixed mesodermal tumors reported from any one institution to date. Symmonds and Dockerty in 1955 reported on 19 cases that were seen and studied at the Mayo Clinic from 1910 to 1952, inclusive. We have observed 3 of these tumors in the last 7 years.

Kehrer, in 1906, used the term "mesodermal mixed tumor" for the first time. MacFarlane, in 1935, found more than 100 different terms in the literature describing this lesion and he advocated the term "dysontogentic tumor." Stout, in 1948, introduced the name "mesenchymoma," and, in 1954, Sternberg suggested "malignant mixed Müllerian neoplasm." Most authors, however, prefer to use the term "mixed mesodermal tumor."

The relationship of endometrial and cervical carcinomas to mesodermal mixed tumors in this

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series is unusual. There were 14 endometrial and 123 cervical carcinomas to one mesodermal mixed tumor. Symmonds reported 143 endometrial and 345 cervical carcinomas to one mesodermal mixed tumor. Most observers would expect a higher incidence of endometrial carcinoma than Dr. Krupp and his associates have reported.

It is interesting to note that no patients received previous x-ray or radium therapy for benign bleeding. This is not in agreement with many reports in the literature. Although there is no conclusive evidence that sarcoma of the uterus can be induced by previous irradiation, especially for benign conditions, the incidence rate seems to be too high to be coincidental. This relationship has been noted by Thornton, Carter, MacFarlane, Speert, and others. The relationship of previous irradiation to the subsequent development of a mesodermal mixed

Table I. Prior radiation for benign disease

Series	Total No.	No. radiated	Interval (years)
Speert (1949)	. 6	3	8.3 (average)
Hill (1951)	4	2	10+, 10+
McElin (1952)	2	2	11, 20
Kight (1953)	6	2	6, 5
Symmonds (1955)	19	4	6, 10, 10, 13
Schiffer (1955)	5	1	6
Wolfe (1958)	14	3	8, 10, 13
Total	56	17 (32.9%)	10 years (averag

Table II. Known 5 year survivors

Series	Total reported	No. survived	Extension
McElin (1952)	2	1	Myometrium
Symmonds (1955)	19	4	Myometrium
Carter (1960)	6	1	Uterus
Geiger (1960)	3	1	Myometrium
Miscellaneous*		6	Through serosa—3
			Unknown—3
Total		13	

*Includes Van Franque, Hartfall, Perry, Ober, Ulfelder, and Chesky.

tumor has been noted by a number of essayists (Table I).

The criteria for the microscopic diagnosis of this highly malignant tumor varies with different authors. Histologically, the neoplasm is characterized by the presence of two or more types of tissue. Microscopically, the sarcomatous fraction of this lesion is dominant and consists of two or more heterotopic mesodermal elements, such as mesenchymatous connective tissue, striated muscle, rhabdomyoblasts with or without cross striations, cartilage, bone, or fat. Various epithelial elements may be present.

The prognosis is generally considered to be very poor. The 100 per cent fatal outcome in the 51 cases reported from Charity Hospital, bears this out. However, in recent years, there have been a number of authentic cases reported with survival over 5 years. Apparently many of the patients in this report did not seek medical care until the disease was far advanced. The 5 year or longer survivals, as noted by a perusal of the literature, were all in relatively early cases. However, one patient reported on by Symmonds, who is living and well over 5 years, had tumor infiltration on the posterior uterine wall extending nearly to the serosal surface (Table II).

Complete abdominal hysterectomy and bilateral salpingo-oophorectomy is the minimum primary treatment of this highly malignant tumor. Radical hysterectomy, vaginectomy, and exenteration should also be considered, depending on the extent of the disease. Although this neoplasm is generally considered to be radioresistant, postoperative irradiation should be given. The value of the isolated pelvic perfusion method is experimental and of questionable value.

Dr. A. N. Arneson, St. Louis, Missouri. These tumors are among the most intriguing types of cancers seen in gynecology. Their behavior is dramatic, and their tendency to kill is exorbitant.

There has been a strong attempt to associate origin of these tumors with previous radiation. Yet, when one looks at long-term follow-ups on patients with cervical cancer who have had large quantities of radiation, these tumors appear quite infrequently.

There are some endometrial carcinomas that occur in perhaps one in 1,000 carcinomas of the cervix—that is, patients who develop endometrial cancer after treatment for carcinoma of the cervix. There are occasional rectal cancers that occur in patients treated by radiation for carcinoma of the cervix, and one wonders if previous radiation might be a factor in the etiology of those tumors.

We identify previous radiation for benigh disease with something that has to do with the origin of endometrial cancer, and yet to pinpoint that for proof is extremely difficult. It appears that there are basic factors inherent to the patient at the time she supposedly had the benigh condition for which she received radiation treatment, which led to the eventual formation of the tumor. I think that might be a factor here, rather than a direct action from the previous radiation for benigh disease itself.

When such a patient is found, it is imperative that some additional procedures be done. There may be opportunities for combining chemotherapy with radiation treatment or for combining changes in oxygen tension with radiotherapy.

DR. R. E. SYMMONDS, Rochester, Minnesota. While our incidence is considerably lower than that reported by Dr. Geiger, this may indicate that he has studied his material more thoroughly. If one assesses the entire group of sarcomas of the uterus and studies them by multiple sections

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an te ly. and restudies them by more sections, more and more tumors will be placed in the category of mesodermal mixed sarcomas. It takes only a small area of striated cells or a small area of cartilage to reclassify sarcoma of the uterus as a mesodermal mixed sarcoma.

This point was particularly impressive in our study of patients previously classified as carcinosarcoma. We started with 20 of these, and as we cut more and more blocks we found more and more examples of heterotopic tissue. While our incidence does not approximate his, I am sure if we cut more blocks we will get closer to it.

As far as the metastatic propensity of the tumor is concerned, we have been impressed by the number of patients who have had the tumor confined to the pelvis for many years, with extensive local spread but without production of distant metastasis. Among the 4 patients Dr. Geiger mentioned, who have survived over 5 years, one had an extensive rhabdomyosarcoma involving the entire endometrial cavity and perforating to serosa, and yet for some unexplained reason this patient has now survived 19 years.

The incidence of previous radiation has been noted by us to be 25 per cent. This has been true with the mesodermal mixed sarcomas and it has been true with the carcinosarcomas. The patients with endometrial sarcoma and also our patients with leiomyosarcoma, have had radia-

tion-induced menopause 5 to 20 years previous to diagnosis of sarcoma.

Dr. Krupp (Closing). The incidence of sarcoma of the uterus, leiomyosarcoma, has been just about the same in our institution as the malignant mixed Müllerian neoplasm—i.e., approximately 0.1 per cent.

It is very difficult to assess patient delay. One patient had had abnormal vaginal bleeding for $3\frac{1}{2}$ years before she came to us with an extensive mixed Müllerian neoplasm. The average delay appeared to be on the order of $3\frac{1}{2}$ to 4 months, but we have not published this because we just could not assess it accurately.

It is important to note that in 30 per cent of the last 30 cases the original biopsy specimen was reported as showing carcinoma only, and it was only upon reviewing the slides thoroughly and cutting new sections, even at times getting larger biopsy specimens, that the exact diagnosis was made.

Chemotherapy is experimental. We have no figures yet that would indicate that this is any help. We believe, however, that it is a logical procedure, and with the chemotherapeutic agents that are soon to be developed, we feel it can only help results.

Postmortem examinations were done in approximately 80 per cent of our patients at our own hospital, and node involvement was found in all of these.

Intra-arterial infusions of pelvic tumors with amethopterin

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THE treatment of carcinoma of the cervix at the present time leaves much to be desired in terms of over-all 5 year survival rates. The therapy of carcinoma of the vagina is almost totally ineffective in obtaining permanent cures. It is, therefore, the constant and pressing obligation of every specialist in gynecology to search for means of improving our present methods of therapy and to develop and perfect entirely new concepts of treatment. The study reported in this paper presents a new therapeutic approach to carcinoma of the uterus, cervix, and vagina, involving the prolonged and continuous injection of a cytotoxic drug directly into the blood supply of the tumor. There have been numerous reports of single and sometimes repeated injections of nitrogen mustard and other drugs into a vessel leading to tumor. There has also been much excellent work done with isolation techniques involving an extracorporeal circuit, whereby a limb or a portion of the body can be perfused with a drug for several hours. But it was not until the work of Sullivan, Miller, and Sikes1 at the Veterans Administration Hospital in New York with tumors of the head and

neck that a means was developed of continuously infusing tumors with a poison over a period of days.

This report deals with an adaptation of Sullivan, Miller, and Sikes' methods to pelvic tumors and presents a means of administering any drug directly into the vascular bed of pelvic tumors for a prolonged period of time.

In order to infuse effectively and efficiently a tumor bed in any location, the following four requirements are necessary: (1) the infusate should be injected into one or two arteries from which most of the blood goes to the region of the tumor; (2) most of the blood supply of the tumor should come from the infused arteries; (3) the vessels must be of a size and accessibility to be catheterized with reasonable ease; and (4) the arteries must be able to be sacrificed, if necessary, without serious damage to normal tissues. For treating carcinoma of the uterus, cervix, and upper vagina, these four requirements are easily fulfilled by employing the hypogastric arteries.

Zeit, Hughes, Cahill, and Hamilton² demonstrated that most of the blood flow through the hypogastric artery can be diverted to the uterus, cervix, and vagina by ligating the posterior trunk of the hypogastric artery and also the inferior gluteal artery when necessary. Fig. 1 shows an arteriogram of an intact hypogastric artery. In Fig. 2 the posterior trunk of each hypogastric artery has been ligated and only the anterior trunk are demonstrated. The 6 patients in this

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study had carcinoma of the cervix, endometrium, or vagina and were treated by continuous prolonged infusions of amethopterin through the hypogastric arteries after the posterior trunks of these arteries had been ligated, as shown in Fig. 2. The drug used in this study was amethopterin, because at the present time it is one of the few drugs available that can be neutralized after it passes through the tumor into the general circulation.

Amethopterin* is an anti-folic acid compound which blocks that step in the production of nucleic acid in which folic acid is converted to folinic acid (citrovorum factor).3 This effect of amethopterin is responsible for its antineoplastic action as well as for its toxic manifestations.

Burchenal and Babcock³ demonstrated that when citrovorum factor is given with or prior to amethopterin, toxicity of the latter is decreased. Sullivan, Miller, and Sikes,1 subsequently, gave protracted intra-arterial infusions of amethopterin to a number of patients having squamous cell carcinoma of the head and neck. They found that patients who were given citrovorum factor intramuscularly tolerated several times the 100 per cent lethal dose of amethopterin, and they were able to maintain a great enough concentration of amethopterin in the carcinomas to obtain a marked tumor response. In some patients the cancer disappeared completely although all the regressions were temporary.

The work of Sullivan, Miller, and Sikes¹ is based upon the delivery of a high concentration of a cytotoxic agent to the tumor mass even though all the drug will ultimately pass into the general circulation and be diluted by the total blood volume. At the same time, an antidote administered systemically can be of a concentration in the general blood stream high enough to prevent or modify systemic toxicity, but not high enough to overcome the overwhelming concentration of the cytotoxic agent in the tumor bed. The relation

Fig. 1. Right hypogastric arteriogram showing the most common variant of the hypogastric artery in an adult female. A, Catheter leading into hypogastric artery near its origin; B, hypogastric artery before its bifurcation; C, superior gluteal artery, which in this patient is the only branch of the posterior trunk; D, inferior gluteal artery; E, uterine artery; F, internal pudendal artery. (Courtesy of Zeit, P. R., Hughes, C. R., Cahill, J. J., and Hamilton, J. G., and the Cleveland Clinic Quarterly, vol. 27, pages 119-124, July, 1960; Fig. 1.)



Fig. 2. Bilateral hypogastric arteriogram after both posterior trunks were ligated. The elimination of the gluteal arteries from the hypogastric circulation has directed most of the flow to the region of the uterus, cervix, and vagina. Note also the evidence of the concentration of contrast medium in the region of the bladder. A, Uterine artery; B, internal pudendal artery. (Courtesy of Zeit, P. R., Hughes, C. R., Cahill, J. J., and Hamilton, J. G., and the Cleveland Clinic Quarterly, vol. 27, pages 119-124, July, 1960; Fig. 3.)

^{*}Methotrexate, Lederle Laboratories, Pearl River, New York.

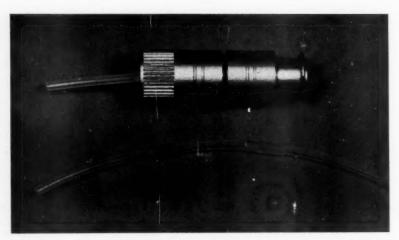
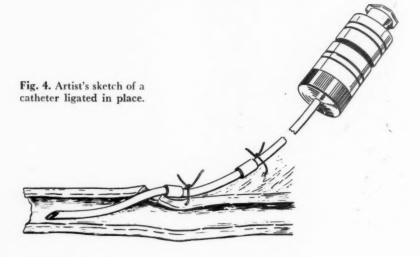


Fig. 3. Both ends of the 20 gauge polyethylene catheter that is prepared ahead of time. The proximal end is fitted with a metal Luer-Lok adapter. The distal end has two cuffs, approximately 1 and 2 inches from the tip, that are made of segments of slightly larger bore polyethylene forced over the catheter.



of the antimetabolite action of amethopterin to citrovorum factor in the production of nucleic acid makes it suitable for use within the framework of the aforementioned concept.^{1, 3-5} Amethopterin is not fixed in tissues and is excreted unchanged by the kidneys in a short time.⁶ Therefore, prolonged and continuous administration is necessary for maximum cytotoxic effect.

Technique

The hypogastric artery is exposed by reflecting a flap of peritoneum from a transperitoneal approach. First, the posterior trunk is ligated with a silk ligature as close to its origin as possible. Two bulldog clamps are then placed on the artery, one clamp near its origin from the common iliac artery, and the other clamp far down on the anterior trunk. The artery is punctured between the two clamps with a 15 gauge needle, and a 20 gauge polyethylene catheter is threaded through the puncture so that its tip lies about 1 inch distal to its insertion. The catheterization is then an almost bloodless procedure, and the elasticity of the vessel

wall usually prevents leakage around the catheter. Arteriograms are taken with use of diatrizoate sodium, 50 per cent, as described in a previous article.2 This is done in each patient to visualize the ultimate distribution of blood in the altered hypogastric tree. Our purpose is to deliver as high a concentration of the amethopterin as possible to the tumor bed and, equally important, to deliver as little of the drug as possible into the general circulation without passing through the tumor. The catheter is secured by passing a silk suture through the superficial layers of the vessel wall proximal to the site of the puncture and tying the suture around the catheter above the first of two cuffs shown in Figs. 3 and 4. A second suture is placed in perivascular tissues and tied above the second cuff (Fig. 4). The other end of the catheter is then threaded extraperitoneally under the lateral parietal peritoneum and is brought to the surface through a stab incision in the abdominal wall. The site of catheterization is carefully checked for leakage and the peritoneum is closed over the vessel.

The catheter is filled with heparin solution and capped. Postoperatively it is connected to an apparatus containing a pump that will deliver a constant slow flow of infusate. The infusate is 25 mg. of amethopterin and 50 mg. of heparin in 1 liter of 5 per cent dextrose in water; the pump is regulated to deliver 1 liter of this solution into each catheter every 24 hours. At the same time the infusion is started, a dosage of 6 mg. every 4 hours of citrovorum factor* is given intramuscularly and is continued through 48 hours after the infusion has been stopped. The infusion is continued until toxic manifestations require discontinuation of amethopterin. During the infusion the patient's general condition is assessed daily by white blood cell counts, accurate fluid intake and output records, and frequent determinations of blood urea and serum electrolytes. When the infusion is stopped, the catheters are capped for several days to allow a clot to form in

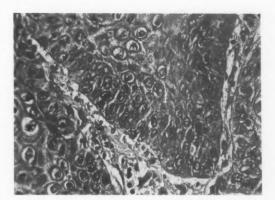


Fig. 5. Tumor of Patient 1 before first infusion. Vaginal biopsy. (Original magnification ×450.)



Fig. 6. Tumor of Patient 1 at end of first infusion. Vaginal biopsy. Note massive necrosis and ghost cells with occasional intact nuclei still present. (Original magnification ×450.)

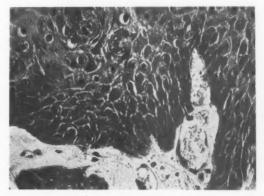


Fig. 7. Tumor of Patient 1 one month after first infusion. Vaginal biopsy. Note marked cellular proliferation replacing old areas of necrosis. (Original magnification ×450.)

^{*}Leucovorin, Lederle Laboratories, Pearl River, New York.

their tips and then cut at the skin and allowed to retract beneath the surface.

Results

Table I summarizes the history, therapy, and results for the seven intra-arterial infusions reported. Two of the patients are discussed now in some detail.

Before pelvic infusion Patient 1 was bedridden because of severe pelvic and perineal pain. Intravenous urograms showed partial obstruction of both ureters, more severe on the right. Intra-arterial amethopterin was administered in December, 1959, through both hypogastric arteries until mild toxic symptoms developed. Biopsy specimens taken before and at the end of therapy are shown in Figs. 5 and 6. Intravenous urograms 2 days after therapy showed that obstruction to the left ureter had disappeared completely, but obstruction to the right ureter persisted.

One month post infusion, the patient was entirely free of pain and able to do her own housework, but biopsy revealed microscopic evidence of marked tumor regeneration (Fig. 7). Two months after therapy she was still without symptoms, but there was obvious gross tumor regrowth and recurrence of the left hydroureter. Cystoscopy revealed growth of tumor through the bladder floor, and a second infusion was done through the right hypogastric artery only. (The left hypogastric artery was completely thrombosed.) Soon after this infusion, a vesicovaginal fistula developed because of necrosis of the tumor that had previously penetrated the bladder floor.

For the next 5 months the patient was given 15 mg. of oral amethopterin per day for 5 consecutive days each month. During this time she was gaining weight and doing light housework. Her only complaint was urinary incontinence, and, consequently, in July, 1960, bilateral cutaneous ureterostomies were done. Exploration of the pelvis at that time revealed tumor present com-

Table I. Summary of pertinent data for 6 patients treated with intra-arterial amethopterin

Pa-	Microscopic				Res	ults
tient	diagnosis	Previous treatment	Indications	Dosage	Subjective	Objective
1	Squamous cell carcinoma of vagina	Radium, cobalt ⁶⁰ , chlorambucil	Pain	325 mg. in 6½ days	100% for 8 months	50% for 2 months
			Tumor regrowth	100 mg. in 4 days	None	50% for 5 months
2	Squamous cell carcinoma of cervix	Incomplete opera- tion, cobalt ⁶⁰ , epidural blocks	Pain	150 mg. in 3 days	Died of infection toxi	n secondary to city
3	Adenocarcinoma of endome- trium	Incomplete opera- tion, extensive x-ray, transvaginal x-ray	Edema and pain	180 mg. in 4 days	Transient, 50% for less than 1 month	50% for edema for less than 1 month
4	Adenocarcinoma of endome- trium	Operation, trans- vaginal x-ray, cautery of vaginal growth	Pain	250 mg. in 5 days	None	None
5	Squamous cell carcinoma of cervix	Radium, extensive x-ray	Edema and pain	350 mg. in 7 days	100% for 3 months	25% for 3 months
6	Undifferentiated carcinoma of cervix	Cobalt ⁶⁰	Pain and bleeding	350 mg. in 7 days	Too early	to evaluate

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parable in extent to that found before the first infusion.

Patient 2 had intractable hip and leg pain. Intravenous urograms showed a nonfunctioning right kidney, but blood urea was normal. One month prior to infusion urea clearance was 55 per cent of normal. In spite of the reduced kidney function, hypogastric infusion was carried out, but by the third day of infusion there was rapid development of severe toxic symptoms. The infusion was stopped, but in spite of increased amount of citrovorum factor, massive antibiotic therapy, and whole blood transfusions, the patient died of overwhelming infection. Prior to death the white blood cells were too few to count. At autopsy a moderate necrosis of tumor (Fig. 8), marked hypoplasia of the blood-forming elements of the marrow, ulceration of the oral and esophageal mucosa, and necrotizing nonreactive bronchopneumonia were found.

These 2 cases are presented in detail to illustrate the best result obtained and the one fatal complication. The results in the 6 patients were: 2 (Patients 1 and 5) had excellent subjective response; one (Patient 2) died as a direct result of the therapy; 2 (Patients 3 and 4) showed no appreciable effect of the therapy (each of these had adenocarcinoma); and one was treated too recently to evaluate results. Only in Patient 2 was there any reason to believe that a patient's life expectancy was shortened.

Comment

All antimetabolites interfere with the formation of nucleic acids and, hence, prevent cell reproduction. Cells reproducing most rapidly will therefore be most damaged by amethopterin, and neoplastic cells, because of their growth characteristics, are most severely affected. In the same way, the hematopoietic system, the gastrointestinal mucosa, and other rapidly reproducing normal tissues are also susceptible to the destructive effects of amethopterin. Schoenbach, Greenspan, and Colsky⁷ reported the occurrence and order of appearance of the various toxic manifestations as follows: ulcerations of the oral

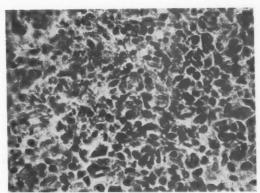


Fig. 8. Tumor of Patient 2 at autopsy 2 days after completion of infusion of less than 150 mg. of amethopterin. Note moderate degree of cell destruction. (Original magnification ×450.)

mucosa, leukopenia, and thrombocytopenia. In our experience with amethopterin given intra-arterially and over relatively short periods of time leukopenia often appears without mouth ulcerations, or the two may appear simultaneously. Three patients had a fairly severe febrile reaction beginning about the third day of therapy. This reaction was not reported by Sullivan and associates1 in patients treated for head and neck carcinomas, nor was it encountered in 12 patients with head and neck carcinomas treated at the Cleveland Clinic.8 These febrile reactions (in one instance a temperature as high as 104° F.) occurred in the first 3 patients and may have been due to faulty technique incidental to the development of arterial catheterization techniques.

The severe and fatal toxic reaction in Patient 2 emphasizes a point not stressed in previous reports. Freeman⁶ showed that after a single intravenous dose of amethopterin 88 per cent of the drug was excreted unchanged in the urine in the first 6 hours. He also pointed out that in 2 patients with renal insufficiency high concentrations of amethopterin remained in the blood plasma for 2 weeks and that higher initial concentrations of amethopterin were obtained in these patients than in patients with normal renal function. The rapid development of toxicity was probably due to the reduced renal function. We now feel strongly that a patient

with a phenolsulfonphthalein test result of less than 25 per cent in 15 minutes is not a suitable subject for amethopterin therapy. It should be pointed out, however, that many patients with one nonfunctioning kidney have normal kidney function and will readily eliminate the drug even though massive doses are given.

The immediate effect on the tumor is a massive necrosis, which is apparent microscopically by the third day of therapy. In Patient 1, from whom repeated biopsies could be easily obtained, the necrosis was progressive during the infusion, but those cells which were still viable at completion of the therapy apparently recovered promptly. One month after the infusion the tumor again had the microscopic appearance of healthy, growing carcinoma (Figs. 5 to 7).

Conclusions

The procedure described is an experimental one and is presented primarily as an evaluation of a new method of administering drugs in high concentration to pelvic carcinomas. Secondarily, we are presenting results in 6 more patients treated with intraarterial amethopterin and intramuscular citrovorum factor.

We have demonstrated to our satisfaction that the hypogastric arteries can be successfully used to deliver a high concentration of a drug to the uterus, cervix, upper vagina, and pelvic floor and walls. The surgical procedure involved is of much less magnitude than pelvic exenteration, radical hysterectomy, node dissection, and other extreme operations used and proposed for advanced carcinoma of the pelvis. The initial technical

difficulties of placing and securing the catheters have been resolved, and the actual administration of a drug through the catheters can be managed by routine nursing personnel once the pump is properly set in operation. Careful physician observation and supervision, however, is mandatory, and the continuation of infusion must be determined on a day-to-day basis.

At the present time there is no specific anti-neoplastic agent that is not highly toxic. Amethopterin does have the advantage of having a counteragent in citrovorum factor that will partially prevent its cytotoxic action, but the results obtained with this drug are of too short duration to warrant its general use as a palliative measure.

In our opinion, however, a method of infusion has been developed which can be used when more specific and better agents become available.

Summary

Six patients with carcinomas of the cervix, uterus, or vagina that persisted or recurred after conventional surgical or radiation therapy were treated by continuous infusion of amethopterin into the hypogastric arteries. Citrovorum factor was administered intramuscularly to prevent generalized toxic manifestations. Hypogastric arteriograms in each case demonstrated evidence of flow of the concentrated drug directly to the tumor. For this therapy, normal or nearly normal renal function is an absolute prerequisite. The immediate effect of the hypogastric intra-arterial infusion on the tumor is profound necrosis, but any neoplastic cells not completely destroyed apparently begin to recover as soon as therapy is stopped.

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Discussion

Dr. WILLIS E. BROWN, Little Rock, Arkansas. The authors offer a relatively new technique. We have conducted similar experiments, reports of which are now in press. It appears suitable to describe our experiments and then perhaps discuss the whole concept of regional perfusion and chemotherapy.

Studies in cellular metabolism by Warburg and many others have suggested that cancer cells were deficient in oxidative phosphorylation and that intoxication of the cytochrome oxydase might offer an effective method of controlling malignant cells, since they would be unable to recover from such intoxication, while the normal tissue might.

Extensive studies in our laboratory were carried out with one of these agents, sodium cyanide, on mice, rats, dogs, and monkeys. We observed prolongation of life of transplanted sarcoma ascites in rats. The control animals died within 18 days after inoculation, and those treated by various systems of cyanide had a longer life.

We then turned our attention to spontaneous tumors in dogs and results similar to those obtained by Dr. Zeit were found. In canine mammary tumors, cyanide produced major necrosis, as was demonstrated by Dr. Zeit.

We then turned our attention to the use of regional perfusion, and we developed systems not too different from his. Our two methods included canalization of the hypogastric arteries, and retrograde canalization of the aorta above its bifurcation. By the use of retrograde catheterization coming above the bifurcation of the aorta and with pneumatic cuffs about the femoral artery, we were able to obtain reasonably good concentration of dye. By alternating the two sides we were able to infuse these patients at weekly intervals. Therefore we have two sets of studies, one dealing with single, massive infusion and the other with weekly infusions.

Our experience with patients is totally unsatisfactory. All of the patients but one are dead, and this one is moribund. We feel, therefore, that the agent is unsatisfactory.

In contemplating chemotherapy, two general types come to mind-the extracorporeal and the systemic perfusion. Since the complete isolation possible in the perfused extremity is not attainable in the pelvis, we have abandoned attempts to carry this out and are using the much simpler methods of systemic perfusion.

The paper by the authors and our own studies have thus explored systemic perfusion through single systemic injections, periodic injections, continuous injections, and intermittent injections. Two agents have been explored and both have been found wanting. The concept of regional perfusion particularly by the systemic route warrants much exploration, because if a proper system can be found it will offer much to the patient with extensive and moderately extensive disease, for it is simple to perform, almost totally without risk, available to almost any community, and very inexpensive.

The potential of this modality is great. Our problem is to find a suitable agent, with or without antidotes, to discover proper sequences of infusion, and the most favorable environment, such as temperature, oxygen saturation, and radiation, which will provide a clinically useful therapeutic schedule.

The Wertheim hysterectomy for squamous cell carcinoma of the uterine cervix

Thirty years' experience at the Mayo Clinic

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JOSEPH H. PRATT, M.D.

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CONSIDERABLE study and effort have gone into the development of a treatment of choice for squamous cell epithelioma of the uterine cervix. Prior to the use of irradiation, surgical treatment was the sole method available to pioneers such as Clark and Wertheim; they had to accept tremendous mortality, morbidity, and numerous distressing recurrences, even in the cases they considered hopeful. Subsequently, radiation therapy has been thought to demonstrate some superiority over operative methods, although recent reports indicate the increasing importance of radical operative treatment in the management of squamous cell epithelioma of the cervix.

At the Mayo Clinic all patients with malignant lesions of the cervix are seen initially by a medical gynecologist who in large part outlines therapy as well as prescribes the follow-up procedures, whether the treatment be irradiation, operation, or both. Only by being called in for surgical consultation or by direct referral does the surgeon see the patient, and faced by excellent 5 year figures from irradiation alone it would be something

more than human for the clinician not to be somewhat influenced despite well-conceived surgical study programs. As a result of this selection, the number of surgical cases is necessarily limited, making it difficult to present adequately any sort of comparison between irradiation and operation. In the present study no attempt is made to compare the two methods of treatment directly, because the surgical cases, in general, were originally selected either from the younger and healthier patients with lesions that were largely confined to Stages I and II of the international classification or from patients who had an unsatisfactory response to irradiation or had recurrences. This study attempts, instead, to face the facts as fully as possible in an effort to understand how large a segment of patients intelligent surgical therapy should embrace in the over-all therapeutic program for this ailment.

The term "Wertheim hysterectomy" as used in this paper indicates a radical abdominal hysterectomy, bilateral salpingo-oophorectomy, and removal of lymph nodes and lymph node-bearing tissue from the iliac and obturator regions, with full intent of achieving a cure, or the equivalent of this procedure in cases in which previous partial excisions were performed. The term "modified Wertheim operation" indicates radical panhysterectomy without complete nodal dissec-

From the Section of Surgery, Mayo Clinic and Mayo Foundation.

Presented at the Twenty-eighth Annual Meeting of the Central Association of Obstetricians and Gynecologists, Kansas City, Missouri, Oct. 6-8, 1960.

tion, again with the intent of achieving a cure. The latter procedure was done occasionally in the early parts of the period covered by this study, for the most part, although some cases are still handled in this manner. We do not consider the radical removal of the uterus, tubes, and ovaries without dissection of lymph nodes an adequate operation for invasive squamous cell carcinoma of the cervix, except for carcinoma in which invasion is only of microscopic proportions.

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A total of 486 cases encountered from 1930 through 1959 were reviewed; 236 involved Wertheim operations with preoperative irradiation, and 250, Wertheim operations without preoperative irradiation. Five-year survival rates were determined on the 310 traced patients having had Wertheim hysterectomies prior to 1954.

Data presented in this paper will apply only to the 486 Wertheim operations done in the 30 year period 1930 through 1959. The ages of the women in this series averaged 43.1 years. The fact that this average age is somewhat lower than had been expected clearly points to the need for maintaining a high index of suspicion irrespective of age, and it re-emphasizes the value of major cancer-screening efforts. Practically all patients were multiparous, averaging about 2 children each. In 14 cases the lesions were associated with pregnancy or the early postpartum period. In 20 cases the lesions were found in a cervical stump.

Classification

All cases in this study were originally classified clinically into stages according to the criteria of the international classification (Table I). A separate division was created in this series for early Stage I (E-I) tumors. Early Stage I lesions were always classified on a microscopic basis when the pathologist, after studying multiple sections, noted that stromal invasion was nowhere of greater than microscopic proportion. Thus, the 16 cases of Stage 0 lesions and the 45 cases of early Stage I lesions in this series were finally classified on the basis of pathologic data even though preoperatively both of these groups were clinically classified as invasive lesions. Our reason for reclassifying these two groups of patients was to avoid the possible inaccuracy of clinical overstaging. This rigid categorization has been useful in the present study, but it falls short of being of scientific comparative worth, since complete pathologic analysis of the cervix by conization was not done on all patients initially treated by irradiation and subsequently receiving surgical treatment.

Operability

In this series the most common criterion for inoperability was the presence of carcinomatous involvement of the upper abdominal or midabdominal aortic lymph nodes. In-

Table I. Distribution according to stage of disease and involvement of lymph nodes

	Total series			With irradiation before operation			Without irradiation before operation		
	Total	With posi	tive nodes	Total	With post	tive nodes	Total	With post	itive nodes
Stage	patients	Patients	Per cent	patients	Patients	Per cent	patients	Patients	Per cent
0	16						16		
E-I	45			9			36		
I	222	26	11.7	78	9	11.5	144	17	11.8
II	161	39	24.2	116	28	24.1	45	11	24.4
III	35	13	37.1	26	10	38.5	9	3	33.3
IV	2	1	50.0	2	1	50.0	700 470		-
Not stated	5	1	20.0	5	1	20.0			
Total	486	80	16.5	- 236	49	20.8	250	31	12.4

deed, most of the inoperable lesions-8 per cent of cases—observed during the period 1951 through 1956 were deemed so because at operation the aortic lymph nodes were found to be involved. These cases in which Wertheim operation was planned and abandoned are important in the consideration of the incidence of lymph-node metastasis, since this figure must be added to the percentage of involved lymph nodes reported for the completed operation to find the actual percentage of carcinomatous nodes in surgically treated squamous cell epithelioma of the cervix. However, this figure obviously does not apply to the present study of completed Wertheim operations.

The surgical anatomy of the retroperitoneal abdominal aorta has become so familiar in the past few years that an extension of the Wertheim operation is entirely feasible and may be accomplished in much the same fashion as the aorta is exposed for segmental resection. This procedure, which is relatively simple and rapid, exposes the aorta through a peritoneal incision up to the ligament of Treitz and provides easy access for the stripping of the nodes from the level of the renal vein and pancreas to the bifurcation of the aorta.

It should be stated that the determination of true operability is difficult in a situation in which the surgeon does not see every case of carcinoma of the cervix. Only about 20 per cent of all carcinomas of the cervix encountered at the Mayo Clinic were treated by operation in the years 1940 to 1948 inclusive; since that time the average has been about 30 to 40 per cent.

Primary Wertheim operation

As shown in Table I, the majority of lesions were classified in the lower stages of the disease, as expected. When an active cervical cytology department is available, it becomes increasingly evident that earlier and earlier lesions can be found, and it is the patients with such lesions whom we regard as ideal candidates for primary surgical treatment. Of the 196 patients classified clinically as having Stage I lesions, 36 proved to have

very early or microscopic invasion. In 16 other cases the lesions were labeled "in situ" or "Stage 0 carcinoma" after histologic study. In all of these 52 patients the disease was controlled successfully with radical hysterectomy and probably could have been handled successfully with a lesser procedure, as the likelihood of lymph node metastasis is remote, in our experience. In only 12.4 per cent of the entire 250 cases in which the Wertheim operation was the primary treatment were the regional lymph nodes involved. According to the stage of disease, there was no involvement in Stage 0 or early Stage I, 11.8 per cent involvement in Stage I, 24.4 per cent in Stage II, and 33.3 per cent in Stage III.

Five-year survival studies were made for the primary Wertheim operations. The overall 5 year survival rate in 165 traced cases from 1930 through 1953 was 85.5 per cent.

Wertheim procedure with preoperative irradiation

The present program of preoperative or definitive irradiation has been outlined as follows for use at this institution: radium treatment, as interrupted dosages to the cervix approaching 7,300 mc. hr., and roentgen therapy, a total of 2,000 to 2,200 r (air) through each of two anterior and two posterior ports to the pelvic walls.

Radiation of this magnitude increases somewhat the surgical hazard in various obvious and hidden ways: by reducing tissue viability, by decreasing effective vascularity, and by freezing the dissection planes. The decision whether or not to operate is therefore made jointly, by the roentgenologist, the gynecologist, and the surgeon. The principal reason for electing supplementary excisional therapy was, in the main, the desire to give the patient maximal therapeutic help, but in a number of cases, continued bleeding, obvious radioresistance, or recurrence dictated supplemental surgical therapy.

A total of 236 patients received irradiation preoperatively about 3 months before the Wertheim hysterectomy. These cases are listed in Table I. In all but a few instances, a complete irradiation regimen had been pro-

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vided either at the clinic or elsewhere. It should be noted from the table that more Stage II lesions were present in this group than in the primary Wertheim group. Hence, although the over-all 5 year survival or nodal involvement rates cannot be compared, the rates can be compared for the various stages of the disease. In such a comparison it is highly interesting to note that in cases in which preoperative irradiation was employed, stage for stage the incidence of metastatically involved lymph nodes was similar to that in the nonirradiation group.

It must be considered that a few microscopically invasive lesions treated by irradiation were probably completely controlled prior to operation, and indeed, in the light of our present thinking, these patients were probably overtreated. However, changes in point of view, these cases deserved inclusion in this study. Also, routine conization of these very early lesions was not done until the later years of the study, and it is possible that a few early invasive lesions were included in the full Stage I figures. To clarify the matter at the outset, it should be stated that irradiation, radical operation, or a combination of these procedures is not our choice of therapy unless a degree of invasion is present that is of more than microscopic proportions. The line for this differentiation is extremely fine and very close cooperation and trust must exist between the departments of pathology and surgery.

Additional information to be gained from this study relates to residual malignant disease after irradiation. In 79 cases evidence of tumor remained after irradiation. In 30 cases the lesion occurred only in the cervix, in 12 it was present in the cervix and regional lymph nodes, and in 37 it was found only in the lymph nodes. Stated differently, of 49 patients with positive lymph nodes, only 12 had discernible cervical residua. We believe, therefore, that absence of cervical residual disease does not permit accurate prediction of whether or not the malignant process has been controlled. In this significant but small group a few patients may have received incomplete irradiation, but the majority must probably be classified as having had radioresistant lesions. Although we have been unable to demonstrate predictable tissue response or sensitivity to irradiation in our laboratories, it is hoped that some day we may have available a method for accurate determination of which tumor will respond to radiation therapy and how well it will respond.

Combined groups of Wertheim hysterectomies

For the over-all picture, a study of both groups, namely, those patients given and those not given preoperative irradiation, is of some help. In recognition of the possibility that changes took place in radiation or surgical technique during the rather long period covered in this study, the combined groups were first reviewed in their entirety (Table I) and then separated according to decades.

Involvement of lymph nodes. The over-all involvement of lymph nodes in the 486 cases was 16.5 per cent. These cases represent Wertheim operations that were completed and do not include those cases in which the lesions proved inoperable when the abdomen was explored. No involvement of nodal tissue was found in the 61 cases of carcinoma in situ and early Stage I lesions. As we have already observed, the early invasive Stage I lesion is a near relative of Stage 0 carcinoma and like it should betoken a highly favorable outlook. This special group of cases has become the subject of continued study, and a special report is forthcoming. Full Stage I carcinoma involved nodes in 11.7 per cent of cases, Stage II carcinoma involved them in 24.2 per cent of cases, and Stage III carcinoma demonstrated nodal extension in 37.1 per cent of this small group of cases. Although a slight difference in the incidence of involved nodes in the irradiated and nonirradiated groups was reported earlier, the final, larger group now shows nodal involvement to be similar.

Unfortunately, when the cases in which involved lymph nodes were present were analyzed by decades, the numbers were too small to be of statistical significance. How-

Table II. Metastatically involved lymph nodes

Nodes involved	No. of patients		
Obturator	35		
Iliac	9		
External iliac	15		
Internal iliac	1		
Parametrial	3		
Broad ligament	1		
Sacral	1		
Multiple	15		
Total	80		

ever, informal breakdown in this manner did suggest that the high doses of irradiation used more recently lower the incidence of metastasis to regional nodes.

Location of lymph nodes with metastatic involvement (Table II). The preponderant involvement of the obturator group of nodes agrees with the results of other authors and points up the importance of completely stripping the obturator fossae of recognizable nodes and of node-bearing tissue. The value of removing these lymphoid structures becomes apparent when the figure of 45.5 per cent salvage rate for 5 years is noted in those cases in which positive lymph nodes were found at operation. These results should help to offset surgical reluctance due to the risk of some increase in postoperative complications. Of 24 patients with lymph node spread who had primary Wertheim operations 5 or more years before our follow-up, 14 (58.3 per cent) were alive 5 years after operation. Of 30 such patients having had preoperative radiation therapy, 10 (33.3 per cent) survived the 5 year period, although it should be noted that there was a much larger proportion of Stage II and Stage III carcinomas in this group as compared with that in the nonirradiated patients.

Technique of operation

The operative technique of Wertheim hysterectomy presents little difficulty for the pelvic surgeon. In our practice, mere details offer the variance, even though each surgeon is free to pursue his own ideas and approaches. Foremost among the differences are the closure of the vaginal vault and the occasional preservation of ovarian tissue for young women with relatively early and localized disease. Practically speaking, the operation amounts to the complete stripping of areolar, lymphoid, and fatty tissue from the common, external, and internal iliac vessels, the obturator fossae, and the internal femoral ring. This tissue is not removed in one segment or necessarily en bloc with the uterus. Radical hysterectomy follows, including removal of both tubes and ovaries. Parametrial and paravaginal ligaments are severed as close to the pelvic walls as possible, and approximately 3 to 5 cm. of vagina is removed. Preservation of the obliterated hypogastric vessels is planned but not always accomplished. After removal of the reproductive organs, all surfaces are reperitonized, in most cases by utilizing redundant sigmoid. Bilateral fenestrated suction catheters are led from the obturator fossae retroperitoneally through stab wounds in each lower abdominal quadrant.

As with so many cancer operations, the surgeon must be alert at every moment to the extent of the malignant process, and he must be prepared to alter his procedure if unexpected projections of the disease are discovered. Thus, accurate preliminary abdominal exploration is an important part of the surgical procedure; it must include palpation of the upper portion of the abdomen, the liver, and the region about the abdominal portion of the aorta. We ordinarily begin the operation on the more difficult side, not committing ourselves until resectability is ascertained but always being in readiness to extend the operation to exenteration if that becomes necessary. During the period of this study our preference was to preserve the bladder by performing partial or segmental resection rather than cystectomy if the lesion appeared to be firmly attached to the bladder or actually involved a small portion of it.

Morbidity

Although every attempt is made to handle tissue delicately, to reperitonize thoroughly and to achieve proper hemostasis, some mor961

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bidity must be expected with this operation. So often it is the patient who is expected to do best who runs the gamut of complications. A strict definition of a morbid course has been used at the Mayo Clinic, based on an elevation of temperature to 100.4° F. or higher on any 2 days subsequent to the first 24 hours after operation. By this criterion, approximately 196 patients (40.3 per cent) experienced a morbid course. However, it is noteworthy that the patients were out of the hospital in an average of 16.1 days, although 16 patients spent from 40 to 78 days in the hospital.

Most major complications were related to the large region of denudation and dissection, scarring of or nonlethal damage to the ureters, impingement on the blood supply, and infection of or lethal damage to ureters, bowel, or bladder. Serious complications were more common in the group receiving irradiation preoperatively (Table III). For example, those patients who had preoperative irradiation had an incidence of postoperative fistula of 11.9 per cent; the incidence was 3.2 per cent for nonirradiated patients. The increased incidence of such complications should in no wise deter performance of necessary surgical procedures, but our experience indicates that the combination of preoperative radiation and radical operation should be avoided as a routine procedure.

We have noted a significant reduction in complications, including seroceles, since suction drainage was initiated approximately 2 years ago. A fenestrated catheter is brought out extraperitoneally through a stab wound in each lower abdominal quadrant. Gomco suction is used, at 90 mm. Hg, until drainage becomes minimized, usually in 2 to 5 days; the catheters are then removed. We have associated this removal of potential culture medium with a lower incidence of pelvic infection and fewer postoperative fistulas.

Mortality

The brighter side of the immediate postoperative picture is a respectable mortality rate of 1.9 per cent. Although this rate was nearly 13 per cent in early years, no postoperative death has occurred since 1943 in well over 350 operations. Considerable credit must go to the generous use of antibiotic drugs and whole blood replacement. Several deaths in the earlier period were no doubt due to lack of adequate agents to combat infection (Table IV).

Survival

In order that the Wertheim hysterectomy may be of real use, it must prove at least as curative as irradiation or offer a reasonable contribution when radiation therapy fails. We all agree that cutting close to or across cancerous tissue at any stage of the operative procedure is not conducive to cure, and this is a real hazard facing the surgeon who attempts a radical operation for advanced disease. Briefly, four avenues of decision are open to the surgeon under such circumstances: (1) he can declare the condition inoperable; (2) he can do less than he desires and perhaps experience later the disappointment of implantation or wildfire spread; (3) he can remove by only narrow margins all visible tumor, with some hope of achieving a cure; (4) he can do a far more radical procedure and take the risk of increased mortality and disability.

The Wertheim operations in this series were done on selected patients who represented somewhat less than 20 per cent of all patients with cervical carcinoma treated at

Table III. Postoperative fistulas or ureteral obstruction

	Irradiation*	No irradiation*
Fistula -		
Vesicovaginal	10(1)	5(2)
Ureterovaginal	11(3)	5 (2) 3 (1)
Complex†	7(1)	0
Ureteral obstruction;		
Unilateral	4	4
Bilateral	5 (4)	1

*Number in parentheses denotes number of patients whose fistula resolved spontaneously.

†Rectovaginal, 3 (1 resolved spontaneously); vesicorectovaginal, 2; ureterorectovaginal, 1; vesicorectoureterovaginal,

‡Postoperative excretory urograms were not done in all cases; hence, these figures may be on the conservative side.

Table IV. Hospital deaths

Cause of death	No. of patients
Pulmonary embolism	3
Shock	2
Uremia	1
Pneumonia	1
Pyelonephritis	1
Erysipelas	1
Total	9 (1.9 per cent

this institution over the long period covered by this study. The patients were generally in good condition and risks were physiologically and surgically low.

In spite of the limited size of this series, it is rewarding to note that excellent survival figures resulted when follow-up studies were tabulated. Informal survival figures, by decades, unfortunately were not statistically significant.

Total group. A total of 321 patients were operated on prior to Jan. 1, 1954, and were therefore available for 5 year studies. Of these, 310 patients (96.6 per cent) were contacted directly or indirectly and 81.9 per cent of the 310 patients were found to be living 5 or more years after operation. All 35 patients in the Stage 0 and early Stage I groups survived; the survival rate for 5 years or more among the 143 patients with Stage

I epithelioma was 87.4 per cent; that for the 109 patients with Stage II disease was 74.3 per cent; and the rate for the 20 patients with Stage III disease was 60.0 per cent (Table V).

Preoperative irradiation. Of 149 patients with preoperative irradiation who were operated on prior to 1954, 145 were traced. Of these, 90.4 per cent with Stage I disease survived 5 years, as did 71.6 per cent of those with Stage II disease, and 66.7 per cent of those with Stage III lesions. The 5 year survival rate for the entire group was 77.9 per cent. The total figure for this group should not be compared with that for the following group, in which operation was the primary treatment; however, a stage-by-stage comparison is possible.

Primary surgical treatment. Of the 172 patients originally in this group, 165 were traced for study of 5 year survival rates; 85.7 per cent of the patients with Stage I lesions were alive, as were 80.0 per cent of those with Stage II disease and 50 per cent with Stage III lesions.

Special groups. Twenty patients had had radical removal of the cervical stump, but only 12 were treated prior to 1954; of these, 10 patients were alive after 5 years, including 3 with microscopically invasive lesions.

Table V. Five-year survival rates by stage and treatment

	Total series			Wit	With irradiation prior to operation				Without irradiation prior to operation			
	Pa	utients	Lived 5 years opera	after		tients	years	or more after ation	Pa	tients	years	or more after
Stage	Total	Traced	Pa- tients	Sur- vival rate (%)*	Total	Traced	Pa- tients	Sur- vival rate (%)*	Total	Traced	Pa- tients	Šur- vival rate (%)*
0	13	12	12	100.0					13	12	12	100.0
E-I	25	23	23	100.0	4	4	4	100.0	21	19	19	100.0
I	147	143	125	87.4	52	52	47	90.4	95	91	78	85.7
II	112	109	81	74.3	77	74	53	71.6	35	35	28	80.0
III	21	20	12	60.0	13	12	8	66.7	8	8	4	50.0
IV	2	2	0		2	2	0	-		-		-
Not stated	1	1	1		1	1	1					
Total	321	310	254	81.9	149	145	113	77.9	172	165	141	85.5

*Based on traced patients. Inquiry as of Jan. 1, 1959. Nine hospital deaths are excluded from the calculation of survival rates.

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Fourteen patients had been pregnant or were in the immediate postpartum state. Eight operations were performed prior to 1954. Of these 8 patients, 6 survived 5 years, including 3 with microscopically invasive or in situ lesions.

Comment

It is quite apparent that we cannot, on the basis of these studies, compare radiation treatment of cervical carcinoma with surgical treatment. On the basis of the 5 year survival rates of 87.4 per cent in Stage I and 74.3 per cent in Stage II carcinoma and of reports of similar results in the literature, it is evident that surgical treatment offers a good chance of cure to the patient with Stage I or Stage II lesions. Operation provides these additional advantages: (1) it permits direct exploration; (2) it is adaptable to unexpected situations; (3) it utilizes precise knowledge of the distribution of lymph nodes and makes possible accurate pathologic examination of the tissues; (4) it permits removal of the cervix, a common site for local recurrence; and (5) it allows the preservation of ovarian tissue in young patients with early lesions. We believe, therefore, that primary Wertheim hysterectomy should not be excluded without specific reason. The mortality rate is very low in all reported series of cases. The morbidity has been thought to be a definite drawback, yet the average hospital stay in our series was 16 days, and many patients were home before then. Of the 36 instances of fistula and 14 of ureteral obstruction among the 486 patients, only 8 of the fistulas (of which 3 healed spontaneously) and 5 late ureteral obstructions occurred in the nonirradiated group.

We would not, of course, advocate radical surgical treatment for all patients. All therapy must be clinically individualized, but we do feel strongly that surgical management in Stage I and early Stage II disease has proved an excellent mode of therapy.

Summary

Thirty years' experience with the Wertheim hysterectomy as primary or secondary treatment for squamous cell epithelioma of the uterine cervix has been summarized.

A total of 486 completed operations were reviewed, 236 with preoperative radiation and 250 without preoperative radiation. The majority of these operations were performed for malignant disease classified as Stage I or II.

Lymph nodes were involved with metastatic disease in about the same incidence whether or not the patient received preoperative radiation.

According to the strict criteria applied, 40 per cent of patients had a morbid course, although the average hospital stay was only 16 days. Urinary fistulas occurred in 11.9 per cent of patients having had preoperative radiation and in 3.2 per cent of patients having received primary surgical treatment.

The 5 year survival rates for the 321 patients on whom follow-up information was available were 81.9 per cent for the entire group, 87.4 per cent for patients with Stage I disease, 74.3 per cent for those with Stage II lesions, and 60.0 per cent for patients with Stage III disease.

Discussion

Dr. Wm. F. Guerriero, Dallas, Texas. This report of a large, well-documented series of cases adds much to our knowledge in the surgical therapy of carcinoma of the cervix.

Recent reports, in particular those of Parsons, Cesare, and Friedell¹ and Kelly, Parsons, Friedell, and Sommers,² have crystallized some ideas from which the surgical treatment of this disease can be more adequately approached.

Essentially these ideas are: (1) agreement with Henriksen that the route of spread is more likely to be in a fore and aft direction than laterally; (2) positive lymph nodes are of increasing importance in prognosis when associated with an increase in amount of tumor at the primary site; (3) positive lymph nodes reflect the overriding of host resistance by tumor and indicates possible spread by other routes as well as by lymphatics;

(4) survival in patients with negative nodes appears to be directly related to the extent of the primary tumor and its removal. A utilization of these ideas will aid considerably in one's use of primary surgical therapy.

Each case must be carefully individualized as to suitable operability and potential survival in relation to the mortality and morbidity resulting from the selected surgical procedure.

The surgical procedure selected should definitely be the one that fits each individual case and in nearly all instances will be made at the operating table. The Wertheim procedure with lymphadenectomy may be suitable in many cases whereas the more extensive exenteration procedures are necessary in other cases. This is because of the above-mentioned ideas which when interpreted mean that unless the primary tumor be totally removed, as well as lymphadenectomy carried out, survival will be low.

This accounts for the fact that Stage I and Ia cases with positive nodes have a higher surviyal than Stage IIa, III, or IV cases with positive nodes since the primary tumor is more extensive and usually not completely removed. Now that surgical techniques have become more refined with such procedures as adequate urinary diversion, the employment of the exenteration procedures in Stages IIa, III, and IV could conceivably afford a better survival in the primary or secondary surgical therapy of this disease.

In conclusion may I quote Kelly and associates²: "Indecision as to the proper form of therapy to employ in the treatment of cancer of the cervix has been fostered by acrimonious discussions concerning the relative merits of surgery or radiation to cure nodes. If the emphasis in treatment is placed on how well the local disease is managed rather than on how effectively lymph node metastases are dealt with, the results of therapy will improve whether surgery or radiation is used. To be successful therapy must adequately remove or destroy the local disease."

REFERENCES

- Parsons, Langdon, Cesare, Frank, and Friedell, G. H.: Surg. Gynec. & Obst. 109: 279, 1959.
- Kelly, John W. M., Parsons, Langdon, Friedell, G. H., and Sommers, S. C.: Surg. Gynec. & Obst. 110: 423, 1960.

Dr. Richard E. Symmonds, Rochester, Minnesota. Whatever one's opinions may be regarding the place for radical surgery in the treatment

of carcinoma of the cervix, I think it is now apparent that it can be performed with an acceptable mortality rate, and certainly with fair results in a selected group of patients.

I would like to say that we consider the morbidity to be too high, especially the incidence of fistulas and especially fistulas in the postradiation cases. Fistulas as a rule are attributable to the unavoidable trauma of surgical procedures and also fibrosis that follows radiation therapy. However, it has been my impression for a number of years that superimposed infection many times is instrumental in the production of fistulas. Ureters and bladders that may be capable of tolerating the ravages of surgery and radiation may well slough when infection is superimposed.

For this reason, during the past 2 years Dr. Pratt, Dr. Welch, and I have developed somewhat similar techniques of pelvic peritonization to cover the denuded bladder base and lower and most important segments of the ureter. During this 2 year period my patients have had no fistulas and no lymphocysts and much of this I attribute to luck and to a certain extent to the system of peritonization.

The bladder peritoneum is sutured to the anterior vaginal wall. This not only covers up the lower segment of the ureter and lower portion of the bladder, but it provides hemostasis in the vaginal cuff. The rectal peritoneum is managed in the same fashion, being sutured to the posterior vaginal wall. There is always sufficient peritoneum available to do this. Following that technique, the broad ligament areas are completely peritonized with sutures so they are airtight, and the rectal peritoneum is brought to the bladder peritoneum.

Following complete airtight closure of the peritoneum we insert suction catheters through separate stab wounds in each groin. The tip of the catheter is attached over the levator fascia so the catheter is not riding on the external iliac vessels and we do not have to fear pressure necrosis.

With the application of suction on the catheters, the peritoneum can visibly be seen to apply itself very closely over the external iliac vessels. The peritoneum has such remarkable healing properties that it adheres in a matter of days, I am sure, and as a result there is no dead space in which lymphocysts can form.

DR. JOHN A. WALL, Houston, Texas. I have just one question. I did not understand clearly whether these patients given radiation were radia-

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ave arly diation failures or whether they were deliberately treated in this manner.

Dr. W. Powell Hutcherson, Chattanooga, Tennessee. Today we seem to have reached an impasse in the treatment of invasive cancer of the cervix. In recent years we have experienced the continued verbal battle of surgical therapy versus irradiation. Regardless of the chosen method, the over-all result is at best a 50 per cent 5 year salvage.

Carcinoma in situ is nearly 100 per cent curable by surgery. The cervix is grossly diseased in 90 per cent of cervices containing carcinoma in situ. Cervical hygiene, socioeconomic status of the patient, and circumcision of the male appear to be significant factors in the development of cervical cancer. If the physician could obtain patient cooperation for semiannual examinations, most cancers could be detected at a preinvasive stage when they are nearly 100 per cent curable.

Our series is small but, I believe, representative. From July 1, 1951, to Aug. 1, 1959, 976 patients were followed annually or semiannually, for from one to 9 years. Five of these patients developed carcinoma in situ. Of these 5, 4 had previous negative smears and a clean cervix 6 months to one year prior to the development of suspicious smears. Only one case of invasive cervical cancer developed during this period, this patient having waited 11 months to follow the advice to have a curettage and biopsy. In the meantime the smears changed from Class II to Class III. During this same period, 7 cases of carcinoma in situ were discovered in other patients at the time of their initial visit or at the time of curettage or conization advised on the initial visit.

Education of the lay public has emphasized that the patient should report to the doctor early symptoms of cancer, such as bleeding and abnormal discharge. Usually these symptoms indicate invasion if cancer is present. Thus, many times the salvage drops from a near 100 per cent to 50 per cent before the patient reaches the doctor. Should we not change our approach to the control of cervical cancer?

Dr. Welch (Closing). Dr. Wall asked why we did so many Wertheim operations on patients who had already had radiation therapy. For a period of time, particularly in the late '40's and early '50's, a program was started in which we attempted to compare a combined type of treatment, namely, radiation plus radical operation thereafter.

The indications for the cases early in the series are difficult to explain. Now, in a large proportion of the surgically treated patients the reasons have to do with the patient herself, the disease condition, and the over-all picture. In approximately one third of these cases operation was probably required because of a change in the pelvic findings over a period of time.

There are three treatments of cervical epithelioma, those three being radiation, operation, or a combination of the two. Perhaps in the future we will have a simple test to determine which lesions demand which specific treatment.

OBSTETRICS

Cigarette smoking and prematurity: a prospective study

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IN 1957, Simpson¹ reported in a retrospective study of 7,499 patients that the incidence of premature births was nearly twice as great for smoking mothers as it was for nonsmoking mothers. Later, in a similar study, Lowe² demonstrated that the mean weight of infants of mothers who smoked regularly throughout pregnancy was 170 grams less than that of infants of mothers who never smoked.

Interest in these findings led to this prospective study with the objective of determining whether or not smoking is a significant determinant of prematurity (birth weight 2,500 grams or less). In addition to smoking habits several other maternal factors were included for investigation. These were (1) work history during the first tri-

mester of pregnancy; (2) education; (3) maternal blood group types, and (4) psychosomatic complaints.

Method

Each year the staff of the Maternity Interviewing Service of the Baltimore City Health Department interviews approximately 6,500 pregnant women who are seeking prenatal care. The purpose of this interview is to determine their financial resources and immediate medical needs. On the basis of their ability to pay for care, these women are either referred to private hospitals for prenatal care and delivery or are accepted for prenatal care in the clinics of the Baltimore City Health Department. Nearly all of the women who receive their prenatal care in health department clinics are registered for delivery at the municipal hospital-the Baltimore City Hospital. Over 98 per cent of these women are Negro.

The patients included in this study consist of all Negro women seen at the Maternity Interviewing Service during 1959 who (1) were scheduled for delivery at the Baltimore City Hospital and (2) received

From the Baltimore City Health Department and the Biometrics Branch, National Institute of Neurological Diseases and Blindness.

The current study was supported by a grant from the Department of Health, Education and Welfare, United States Public Health Service, National Institutes of Health Research Grant B-2154.

prenatal care in prenatal clinics of the Baltimore City Health Department. This selection procedure provided an economically homogeneous group whose members had a similar prenatal and delivery experi-

The information collected in this study came from three sources. The first source was an interview which was conducted at the Maternity Interviewing Service Clinic after it had been determined that a woman met the study requirements. This interview consisted of questions concerning smoking history, work history, education, and psychosomatic complaints. The questions used to develop psychosomatic complaint scores were those proposed by Stouffer and asso-'ciates3 as a part of a neuropsychiatric screening adjunct. Eight per cent of the women were interviewed during the first trimester of pregnancy; 60 per cent during the second trimester, and 32 per cent during the third trimester.

The second source was the prenatal clinic history from which maternal blood group type and initial hemoglobin was obtained. All blood group typing was done at the same laboratory.

The third source, birth and stillbirth certificates, provided the following information: birth weight, sex, plurality, gravidity, mother's age, and the duration of pregnancy calculated from the date of the last menstrual period. By using a cross-reference

Table I. Delivery status

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A.	Pregnancy outcome for women		0.000	
	who were included in study		2,828	
	Single live births	2,736		
	Pregnancies resulting in			
	multiple births	52		
	Fetal deaths	31		
	Abortions	9		
B.	Withdrawn from study		87	
	Reregistered at other hospital	28		
	Not pregnant	22		
	Death before delivery	1		
	Moved from city	4		
	Delivered, birth certificate.			
	not found	12		
	Unknown delivery status	20		
To	otal No. of women interviewed		2.91	5

system between birth and death certificates it was also possible to obtain a record of neonatal deaths that occurred among the study population infants.

In order to determine the consistency of response to the interview a total of 197 patients were reinterviewed on arbitrarily selected days at the time of their visit to a prenatal clinic. The interval between first and second interviews ranged from 2 weeks to 6 months with a median of 10 weeks. With different interviewers, questions on smoking history that led to a classification of smoker or nonsmoker showed 86 per cent agreement; work history showed 89 per cent agreement; education showed 82 per cent agreement. For the classification of psychosomatic scores used in this study the agreement was 85 per cent.

Results

The extent to which the 2,915 women enrolled in the study were successfully followed is shown in Table I. Of the women interviewed, 2,828, or 97 per cent, were delivered either at the Baltimore City Hospital where they were originally registered for delivery, at other hospitals in the city as emergency admissions, or en route to a hospital. The results of the study are based principally on the prenatal information given by the 2,736 women who were delivered of single liveborn infants. A total of 87 women, 3 per cent of those interviewed, were withdrawn from the study for the reasons shown in Table I. A transfer to another medical facility prior to delivery was cause for withdrawal from the study since these women no longer met the requirement of delivery scheduled at the Baltimore City Hospital.

Smoking and prematurity

The study of smoking history and prematurity has been limited to the 2,736 single live births in this series. A total of 92 pregnancies resulted in multiple births, fetal deaths, or abortions. The smokers and nonsmokers with multiple births or abortions were distributed in the same way as those who were delivered of single liveborn infants. The fetal deaths will be discussed later.

A comparison of smoking history prior to pregnancy and at the time of interview (Table II) shows consistency in smoking patterns. In this table a woman was classified as a "smoker" if she smoked every day. All others, the nonsmoker and the occasional smoker, were classified as "nonsmoker." For the 1,563 women who were nonsmokers before pregnancy and at the time of interview the rate of prematurity was 11.2 per cent. A similar rate was observed for the 154 women who smoked before this pregnancy but who were nonsmokers at the time of interview. Only 59 women became cigarette smokers during pregnancy. For this group the prematurity rate was 13.6 per cent. Among women who smoked before pregnancy and at the time of interview, the rate of premature births was 18.6 per cent. Because of the consistency of smoking history, smoking status at the time of interview was the one analyzed.

Table III shows the incidence of prematurity and mean birth weight for the 5 classifications of smoking history ranging from nonsmoker to women who smoked more than one pack per day. The incidence of prematurity increased with the amount smoked from a low of 11.1 per cent for the infants of nonsmokers to a high of 22.9 per cent for the infants of women who at the time of interview smoked more than a pack of cigarettes daily. Fig. 1 shows the relationship between the rate of prematurity and the amount smoked. The prematurity rate for nonsmokers and occasional smokers combined, hereafter called the "nonsmoker group," is 11.2 per cent compared to 18.4 per cent for the "smoking group." According to these figures, there is a 64 per cent excess in the rate of premature birth (that is, birth weight 2,500 grams or less) among the infants of Negro women who smoked

Table II. Number and per cent of premature infants according to mother's smoking history

Smoking history*			No. premature by birth weight	%
Before this pregnancy	At time of interview	Single live births	(2,500 grams or less)	premature
Nonsmoker	Nonsmoker	1,563	175	11.2
Smoker	Nonsmoker	154	17	11.0
Nonsmoker	Smoker	59	8	13.6
Smoker	Smoker	960	179	18.6
Total		2,736	379	13.9

^{*}Occasional smokers are included with nonsmokers.

Table III. Prematurity rates and mean birth weight according to amount smoked

Smoking history at time of interview	Births	Premature births*	% premature	Mean birth weight (grams)	Standard devi- ation (grams)
Nonsmoker	1,547	172	11.1	3,085	555
Occasional smoker (not every day)	170	20	11.8	3,030	535
Less than one-half pack per day	549	92	16.8	2,952	575
One-half to one pack per day	422	84	19.9	2,894	545
More than one pack per day	48	11	22.9	2,855	510
Total	2,736	379	13.9	3,022	570

^{*}Birth weight 2,500 grams or less.

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Table IV. Duration of pregnancy and mean birth weight for nonoperative deliveries according to smoking history

Length of gestation	Nu	ımber	Mean birth weight (grams)		
in weeks	Smokers	Nonsmokers	Smokers	Nonsmokers	
Under 29	22	37	1,955	2,195	
30-31	32	22	2,375	2,475	
32-33	31	63	2,750	2,545	
34-35	77	110	2,680	2,905	
36-37	151	233	2,870	2,990	
38-39	270	484	3,000	3,125	
40-41	202	402	3,140	3,250	
42-43	54	100	3,130	3,360	
44 and over	27	40	3,030	3,265	
Unknown	14	7		•	
Total known	866	1,491			
Mean	38.4	38.7	2,924	3,080	

during pregnancy. Simpson's study showed a similar excess, 48 per cent, at the San Bernardino County Hospital, a hospital which presumably serves women from a similar economic level as the women who are delivered at the Baltimore City Hospital. The mean birth weight of infants of nonsmokers (including occasional smokers) in the present study was 3,080 grams compared to 2,924 grams for the infants of smokers. This statistically significant difference of 156 grams is in close agreement with the nonsmoker-smoker difference of 170 grams reported by Lowe.

The mean duration of pregnancy (excluding operative deliveries) for women who smoked was 38.4 weeks compared to 38.7 weeks for the nonsmokers (Table IV). The similarity of mean pregnancy duration of the two groups is an agreement with Lowe's finding for smokers and nonsmokers. For infants who were classed as premature by birth weight, the mean gestation was 35.1 weeks for the smoking mothers compared to 34.5 weeks for nonsmokers. Evidence that the infants of smokers weigh less than infants of nonsmokers for a wide range of pregnancy duration (Table IV, Fig. 2) suggests a fetal development mechanism rather than early onset of labor. For pregnancies of 34 weeks' duration or more, the mean weight of infants of nonsmokers was consistently greater than the mean for infants of smokers. Lowe reports similar findings for pregnancies of 260 or more days' duration. For pregnancies of less than 34 weeks, the mean birth weights for infants of smok-

Table V. Characteristics of smokers and nonsmokers, similar frequencies*

Smokers		Characteristic	Nonsmoker
No. studi	ed		
1,019			1,717
Age of n	nother		
2	$(0.2) \dagger$	Under 15 years	14 (0.8
296	(29.0)	15-19	504 (29.4
349	(34.3)	20-24	585 (34.1
226	(22.2)	25-29	332 (19.3
	(9.8)		169 (9.8
46	(4.5)	35 and over	113 (6.6
Blood gr	oup type		
249	(24.4)	A	432 (25.1
	(18.5)	В	328 (19.1
471	(46.2)	O	807 (47.0
47	(4.6)	AB	64 (3.7
64	(6.3)	Unknown	86 (5.0
Initial h	emoglobii	n level (grams per	100 c.c.)
18	(1.8)	Less than 8.7	43 (2.5
592	(58.1)	8.7-11.5	1,007 (58.7
314	(30.8)	11.6 or more	545 (31.7
95	(9.3)	Not determined	122 (7.1
Sex of c	hild		
481	(47.2)	Male	867 (50.5
		Female	

*Not significantly different (p > 0.05).

†Percentages.

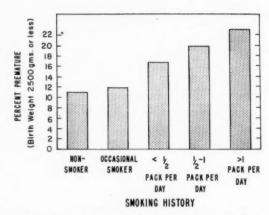


Fig. 1. Rate of prematurity according to smoking history (single live births, Negro, Baltimore).

ers and of nonsmokers were not significantly different.

These results indicate an association between cigarette smoking and the rate of premature birth. It is possible, however, that this is a coincidence resulting from a third factor which is associated with both the frequency of premature birth and the amount of smoking. The possibility of such a relationship has been investigated for several factors.

For the characteristics shown in Table V there is no evidence of a significant difference in distribution between smokers and nonsmokers.

Thus, maternal age, blood group type, initial hemoglobin level, and sex of child are similar for smokers and nonsmokers. Table

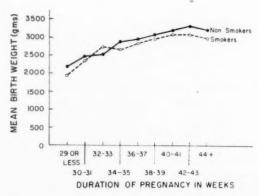


Fig. 2. Mean birth weight and duration of pregnancy (single live births, Negro, Baltimore).

VI shows characteristics for which there are statistically significant differences between smokers and nonsmokers. Thus, for gravidity, work history, education, and psychosomatic complaint scores it is necessary to determine if the smoker-nonsmoker differences in prematurity rates exist for each level of the factors shown in this table.

Gravidity

The rate of premature births among multigravidas who smoke is 18.5 per cent, a figure that is significantly greater than the 10 per cent for comparable nonsmokers (Table VII). The smoker-nonsmoker difference in the rate of prematurity for primigravidas is not statistically significant although the rate for smokers is higher. Mean birth weight in grams is also shown in Table VII. For the infants of multigravidas who smoke, the mean birth weight is significantly less, 194 grams, than the mean birth weight for infants of nonsmoking multigravidas.

Work history

The rate of prematurity according to smoking and employment before or during the first trimester of this pregnancy is shown in Table VIII. For women who worked before this pregnancy there is a significant difference in the rate of prematurity between smokers (19.7 per cent) and nonsmokers (7.6 per cent). A somewhat smaller difference, but nevertheless a significant one, is obtained for women who were not working before this pregnancy. Similar results are obtained for work history during the first trimester. From these findings it follows that the smoker-nonsmoker difference in the rate of prematurity is independent of work history before or during the first trimester of pregnancy.

Education

Prematurity rates according to years of education and smoking history are shown in Table IX for three groups representing women whose education ended in elementary, junior high, or high school grades. Re-

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Table VI. Characteristics of smokers and nonsmokers, dissimilar frequencies*

Smokers		Characteristic	Nonsmok	ers
No. studied				
1,019			1,717	
Gravidity				
161	(15.8)†	Primigravida	341	(19.9)
858	(84.2)	Multigravida		(80.1
Work histor	y			
335	(32.9)	Worked before this pregnancy	487	(28.4
684	(67.1)	Did not work before this pregnancy	1,230	(71.6
356	(34.9)	Worked during first trimester	518	(30.2
663	(65.1)	Did not work during first trimester	1,199	(69.8
Education				
111	(10.8)	Elementary school (1-6 years)	189	(11.0
518	(50.8)	Junior high school (7-9 years)	678	
390	(38.3)	High school or more (10 or more years)	850	1
Psychosomat	ic complaint	score		
248	(24.3)	"Nervous" (five or more complaints)	288	(16.8
771	(75.7)	"Normal" (less than five complaints)	1,429	(83.2

*Significant at p < 0.05.

†Percentages.

Table VII. Prematurity rates and mean birth weight according to gravidity and smoking history

Smoking history Births	-9		Gravi	dity				
		Primig	ravida		Multigravida			
	Births	Premature births	Per cent premature	Mean birth weight (grams)	Births	Premature births	Per cent premature	Mean birth weight (grams)
Nonsmoker	341	54	15.8	2,907	1,376	138	10.0	3,122
Smoker	161	28	17.4	2,909	858	159	18.5	2,928
Total	502	82	16.3		2,234	297	13.3	

Table VIII. Prematurity rates according to work history and smoking habits

		Worked		Did not work		
Smoking history	4	Premature			Premature -	
	No. births	No.	%	No. births	No.	
During month of la	ist menses					
Nonsmoker	487	37	7.6	1,230	155	12.6
Smoker	335	66	19.7	684	121	17.7
Total	822	103	12.5	1,914	276	14.4
During first trimest	er					
Nonsmoker	518	44	8.5	1,199	148	12.3
Smoker	356	74	20.8	663	113	17.0
Total	874	118	13.5	1,862	261	14.0

Table IX. Prematurity rates according to education and smoking history

	Years of education									
	6 years or less			7 to 9 years			10 or more years			
Smoking history	Births	Pre- mature births	% prema- ture	Births	Pre- mature births	% prema- ture	Births	Pre- mature births	% prema- ture	
Nonsmoker Smoker	189 111	18 21	9.5 18.9	678 518	80 98	11.8 18.3	850 390	94 68	11.1 17.4	
Total	300	39	13.0	1,196	178	14.9	1,240	162	13.1	

gardless of the number of years of education reported, a significant difference was found between prematurity rates for smokers and for nonsmokers.

Psychosomatic complaint scores

Investigations by Heath⁴ and Lilienfeld⁵ indicate that there are emotional differences between smokers and nonsmokers. For this reason, 15 questions developed by Stouffer and associates as a part of a neuropsychiatric screening adjunct were used as a part of the study interview. Responses to questions concerning health problems, trouble getting to sleep, trembling hands, fainting spells, nervousness, "heart beating hard," pressures or pains in the head, dizziness, fingernail biting, shortness of breath, sweating hands, sick headaches, upset stomach, nightmares, and "cold sweats" were used to divide the women in this study into two groups. Women who gave 5 or more positive responses to these questions comprised a group for which the psychosomatic complaint score was high. For the purpose of this study these women have been labeled as "nervous." Women who reported fewer than 5 positive responses to the 15 questions, a low score, were called "normal." Table X shows the rate of prematurity for "nervous" and "normal" women according to their smoking history. In both the "normal" and "nervous" groups the rate of prematurity is significantly greater for the smokers; however, the "nervous" smokers have a significantly higher rate of prematurity (23 per cent) than the "normal" smokers (16.9 per cent).

Fetal and neonatal mortality

Fetal and neonatal death rates are higher for infants of cigarette smokers than for infants of nonsmokers. Table XI shows the number of deaths and the fetal and neonatal death rates for the two groups. The difference between the fetal death rate for the smoking group (15.5 per 1,000 births) and for the nonsmokers (6.4 per 1,000 births) is statistically significant. Although the neonatal death rate for infants of smokers (27.5 per 1,000 live births) is greater than the rate for the nonsmoker group (23.3 per 1,000 live births) the difference is not significant.

In a review of previous pregnancies, the proportion of multigravidas who had at least one prior stillbirth was greater for smokers than for nonsmokers.* Of 858 multigravidas who were smokers, 79 or 9.2 per cent had a record of previous stillbirth. Among the 1,376 nonsmoking multigravidas, 99 or 7.2 per cent had had stillborn infants in previous pregnancies. These percentages by themselves are not significantly different; however, the previous stillbirth experience of the smokers appears to be consistent with their adverse experience in fetal and neonatal loss during the pregnancy followed in this study.

Comment

This study of 2,736 pregnant Negro women who were interviewed prenatally and followed throughout pregnancy dem-

^{*}It is not possible at this time to determine the actual prior stillbirth rate since the count of total previous pregnancies has not been processed.

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actual pregonstrates an association between cigarette smoking history and prematurity. Prematurity rates increased with the amount smoked from a low of 11.1 per cent for the nonsmoker (excluding occasional smokers) to a high of 22.9 per cent for women who at the time of interview smoked more than one pack per day. The smoker-nonsmoker difference in prematurity rates prevailed in the presence of several other factors which could possibly have caused a spurious association. Gravidity was an exception. For primigravidas, the smoker-nonsmoker difference in prematurity rates was not statistically significant whereas for the multigravidas it was. The lack of a significant difference among the primigravidas is perhaps related to the fact that in this group there are proportionately fewer heavy smokers than in the group of multigravidas. Among primigravidas only 31 per cent smoked more than one-half pack per day compared to 41 per cent of the multigravidas. It is also plausible that the effect of primigravidity, which tends to increase the rate of prematurity, is greater than the association of prematurity with smoking per

se, thereby accounting for a diminished difference between nonsmokers and smokers.

The similarity of the duration of pregnancy for smokers and for nonsmokers and the smaller mean birth weights for infants of smokers compared to those of nonsmokers, regardless of gestation after 32 weeks, suggests that a fetal development mechanism is involved rather than premature onset of labor.

In appraising the results of this study two possibilities are suggested. The first, as pointed out by Yerushalmy,6 is that "smoking acts as an index to differentiate smokers from nonsmokers on a number of different characteristics rather than as indicating a causal relationship." A second possibility is that smoking has a direct effect which leads to an increased rate of prematurity. For example, smoking might reduce maternal appetite to the extent that it would manifest itself in reduced weight of the newborn infant. Another possibility is that vasoconstriction caused by smoking might have an appreciable effect on fetal nutrition through a decrease in the blood supply reaching the intervillous space.

Table X. Prematurity rates according to psychosomatic complaint scores and smoking history

Smoking history	Psychosomatic complaint score							
	Low—normal			High—nervous				
	Births	Premature births	% premature	Births	Premature births	% premature		
Nonsmokers	1,429	162	11.3	288	30	10.4		
Smokers	771	130	16.9	248	57	23.0		
Total	2,200	292	13.3	536	87	16.2		

Table XI. Number and rate of fetal and neonatal deaths according to smoking history

Smoking history	No. live births	Nu	mber	Death rate		
		Fetal deaths	Neonatal deaths	Fetal deaths per 1,000 deliveries	Neonatal deaths per 1,000 live births	
Nonsmoker	1,717	11	. 40	6.4	23.3	
Smoker	1,019	16	28	15.5	27.5	

From this study there was a reduced prematurity rate among the 154 women who elected to stop smoking during pregnancy. However, there is no evidence that a reduction in prematurity rates could be achieved in a randomly selected group by their curtailing or stopping cigarette smoking during pregnancy. Until the role of smoking and its association with increased prematurity is determined, each obstetrician must decide whether or not to advise his patients to limit smoking.

Summary

Cigarette smoking histories obtained from prenatal interviews with 2,736 Negro women who were delivered of single liveborn infants show that the prematurity rate for smokers was 18.4 per cent compared to 11.2 per cent for nonsmokers (excluding occasional smokers). The rate of premature birth increased with the amount smoked.

This difference was independent of maternal age, blood group type, initial hemoglobin level, sex of child, work history, education, and psychosomatic complaint score. Although a difference in the prematurity rates for smokers and nonsmokers was found for the 2,234 multigravidas in this study it was not found to be significant for the 502 primigravidas.

The evidence presented here is generally consistent with that of retrospective studies conducted in California by Simpson and in Birmingham, England, by Lowe.

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Hemolytic disease of the newborn due to the Good factor

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The existence of blood groups has been known since 1901 when the ABO system first evolved. Levine and Stetson and Landsteiner and Wiener laid the foundations of the vast knowledge of the Rh groups now available and related them as causative agents in hemolytic disease of the newborn. The case reported here presents a new blood factor found during the study of a series of erythroblastotic premature infants. Subsequent detailed serologic studies have indicated that this new blood factor, since called the "Good factor," was present.4

Case report A

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Mrs. H. G., a 28-year-old Negro woman, gravida viii, para vi, who had had one abortion, had been followed in the Woman's Medical College Hospital Prenatal Clinics from the fourth month. She was admitted on Aug. 16, 1958, to the Woman's Medical College Hospital for observation because of previous abnormal obstetric history. She was at that time approximately 61/2 months pregnant and had complained of vague lower abdominal and sacroiliac pains for 11/2 weeks. She claimed that there had been some slight spotting for 2 days and that for 24 hours prior to admission she had severe dizziness and two episodes of actual syncope. She had urinary frequency and past history indicated that cystitis had occurred during 2 pregnancies. Both she and her present husband had blood Type O, Rh positive.

> From the Department of Obstetrics and Gynecology of the Woman's Medical College of Pennsylvania and Hospital.

Her past medical history was not remarkable but she had had "possible bronchopneumonia" in 1952 treated with antibiotics and Asiatic influenza in 1957 treated symptomatically.

Past obstetrical history. She had been married twice and had had 2 normal full-term deliveries during her first marriage. A résumé of the pregnancies follows:

First husband.

1948. Full-term delivery, North Carolina, 5 pounds, forceps delivery, living and well. (Female.)

1949. Full-term delivery, North Carolina, 5 pounds, 7 ounces, normal spontaneous delivery. (Male, killed in automobile accident at age 5.)

Second husband.

1953. Premature delivery at 7 months, Army Hospital, normal spontaneous delivery, 5 pounds, living and well. (Male.)

1954. Premature delivery at 7 months, City Hospital, Philadelphia, 4 pounds, 4 ounces, normal spontaneous delivery. Neonatal death from hemolytic disease, hemoglobin 4.9 Gm. (Male.)

1956. Abortion at 2 months, private hospital, Philadelphia, dilatation and evacuation with transfusion, Type O, Rh positive.

1956. Premature delivery at 7 months, Woman's Medical College Hospital, stiflborn, normal spontaneous delivery, 5 pounds, ½ ounce, no autopsy performed. (Macerated male.)

1957. Premature delivery at 7 months, Woman's Medical College Hospital, stillborn, normal spontaneous delivery. Autopsy performed, intrauterine death, cause unknown. (Male.)

This admission. On admission, August 16, the fetal heart tones were normal and regular at 150 per minute and located in the right lower

quadrant. On August 21, placentography revealed that the placenta was larger than usually seen for the duration of the pregnancy, but normally located. Hematologic studies were: red blood count 2.27 million; hemoglobin level 10.5 Gm.; hematocrit determination 28; reticulocytes 2.8; platelets 122,000; white blood count 6,550. Direct Coombs test was negative; indirect, negative. Rh sensitivities in saline and albumin were also negative. The total bilirubin was 0.50 mg. per cent; 1 minute was 0.15 mg. per cent; indirect, 0.35 mg. per cent.

On August 23 the fetal heart tones became slightly irregular at 136 per minute. The patient was closely watched and on August 24, in light of the irregular fetal heart sounds, cesarean section was elected. The patient was taken to the operating room and under spinal anesthesia a Beck cesarean section was performed. A living baby girl weighing 1,780 grams was delivered; she breathed a few times but died shortly thereafter.

Studies on the baby's blood (which was Type O, Rh positive) were hemoglobin level 5.5 Gm.; hematocrit determination 25; bilirubin level 3.35 mg. per cent.

At this time a blood sample was taken from the husband as well as from the wife. It was found that the husband's serum and the mother's cells caused no abnormal reaction but the mother's serum agglutinated the child's and husband's cells.

Pathology. Description of the postmortem examination of the baby revealed subcutaneous edema of the skin and ascites. There was seen also to be slight splenomegaly with congestion of the spleen on microscopic examination. The chief disease and cause of death was considered as prematurity plus hemolytic disease of the newborn.

Comment

Immunologic studies failed to demonstrate the Good antigen in approximately 1,700 compatible blood specimens. However, the Good antibody was found as a naturally occurring antibody in 6 cases. The antibody did not agglutinate papain-treated cells which demonstrates an immunologic similarity to the MNS and Duffy systems. This serologic activity was found predominantly in the gamma globulin of the 7S class by anion-action cellulose exchange chroma-

tography. The Good antigen is not sex-linked and did not correspond to any of the known blood groups or to the existing antigens Hu, He, Mi^a, Vu, Vr, M^g, C^x, E^w, V, Kp^b, Di^a, Js^a, Levay, Wr^a, Be^a, By, and Sw^a.⁴

Case report B

In June, 1959, Mrs. H. G. again became pregnant—the seventh time since her second marriage. Since the last delivery, the Good factor had been identified in her husband's blood and the fact of her sensitization to it was well established. It was decided jointly by the Obstetric, Hematologic, and Pediatric Services that: (1) the patient would be started on cortisone therapy after the twelfth week of gestation in the hope of suppressing antibody formation; (2) delivery would be accomplished by elective repeat cesarean section as early as possible depending on fetal size but before overt signs of fetal distress; and (3) exchange transfusions would be done in the operating room immediately upon delivery.

Accordingly, on Sept. 29, 1959, at approximately 12 weeks' gestation, the patient was started on dexamethasone 0.75 mg. orally four times daily. The pregnancy was uneventful except for vaginal spotting in the second month, gastroenteritis in the seventh month, and the anticipated progressive Cushing-like changes secondary to the steroid therapy. Anti-Good titers were as follows: 1:8 in October, 1:4 in November, and negative in December, 1959.

On Jan. 27, 1960 (approximately the thirtieth week), the patient reported a diminution of fetal activity such as she had experienced just prior to the death of her previous babies. From clinical examination and x-ray of the abdomen, the baby was thought to weigh about 4 pounds. The patient was delivered that day by Beck cesarean section of a living female infant weighing 3 pounds, 15 ounces, who was immediately given an exchange transfusion. The infant was pale, icteric, and had hepatomegaly. The laboratory studies at birth were: hemoglobin level 7.4 Gm.; hematocrit determination 21; blood smear showed 35 nucleated red cells per 100 white cells; Type O, Rh positive, Good positive, Coombs test was negative, but the baby's cells plus the mother's serum yielded immediate agglutination; total bilirubin 5.3 mg. per cent.

The baby received a total of four exchange transfusions of approximately 400 ml. each and one single transfusion of 40 ml. She was dis-

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charged in good condition 41 days after birth weighing 5 pounds, 91/4 ounces. The mother had an uneventful puerperium and was discharged on the ninth postpartum day with the steroid hormone dosage being gradually reduced.

Comment

The prophylactic value of the steroid therapy in obtaining a viable infant is still definitely conjectural. The induction of labor at the first sign of fetal embarrassment and the use of immediate exchange transfusions may well have been the important factors for fetal salvage in this instance rather than the steroids alone.

Summary and conclusions

A case report (A) of an obstetric patient specifically sensitized to a new blood factor,

the Good factor, present in the husband's blood and reflected by a series of babies with hemolytic disease of the newborn is presented. From this history, one may conclude that the lack of a positive Coombs test on cord blood should not lull the attending physician into a false sense of security. In our particular patient, the antibody was first identified by incubating the mother's serum with the father's and subsequently the child's cells. This relatively simple procedure should be done routinely in all instances of suspected hemolytic disease of the newborn to determine the presence of an isoimmune mechanism in the production of this disorder.

Steroid therapy was employed to overcome this condition in the patient's most recent and successful pregnancy (B). The significance of its use is briefly discussed.

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Adrenal insufficiency in postmature Holstein calves

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ABNORMALLY long gestation periods have been reported in several breeds of dairy cattle.1, 2, 3 In the Holstein-Friesian and Guernsey breeds it is established that the prolonged gestations are conditioned by genetic factors.3, 4 Present indications are that the gene in question is a recessive factor and that the length of gestation is determined by maternal and fetal genotype interactions. Thus, if the gene that determines gestation length is designated as P, gestation length and preparturient physiology is normal if the genotype of the maternal organism is PP or Pp, and that of the fetus is PP or Pp. If the genotype of the cow is Pp and that of the fetus is pp, gestation is prolonged by significant times, and the preparturient physiology of the maternal organism differs from that observed in normal circumstances. The cow does not undergo the usual preparations for parturition. The pelvic ligaments relax minimally or not at all; the vulva does not become edematous or hyperemic; the cervix does not soften and the cervical plug is maintained intact: the udder does not become heavy, and, in primigravidas, it may remain in the virginal state.

Of equal importance is the observation that the behavior pattern of the cow is similar to that of a nonpregnant animal. Even at term the cow that is carrying a fetus doubly recessive for the gene appears to be unaware of her physiological state. She does not become apprehensive or protective, nor does she move away from other animals in the herd in an attempt to seek solitude.

A cow that is heterozygous for the gene in question and bred to a bull heterozygous for the gene may have a normal pregnancy followed by an abnormal one. She may have several normal pregnancies, or she may have consecutive abnormal pregnancies. The critical factor appears to be the genotype of the fetal organism.

It is obvious that maternal unpreparedness at term prevents normal vaginal delivery. In the field, vaginal delivery of the Guernsey calf may occur sometime after term. Since the fetus is dead when found, it is probable that intrauterine death precipitated parturition. Postterm vaginal delivery may occur in the Holstein-Friesian cow, but it is usually fatal to the cow if labor is unassisted because of the poorly dilated vaginal canal and the large conceptus. In our laboratory it is routine practice to deliver the calf by cesarean section.

From the above considerations, it is logical to consider that the physiological events that lead to and terminate in the birth of a fetus at a definite time are controlled by

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In the Holstein-Friesian and Guernsey breeds, where the studies of our laboratory have been made, prolonged gestation is associated with defective fetuses. In brief, the postmature Guernsey fetus is premature in development, resembling a 7 months' fetus.5 Without exception, it exhibits adenohypophyseal aplasia. The Guernsey fetus is alive at delivery, but dies within 10 to 15 minutes. In contrast, the Holstein-Friesian calf is usually large at delivery, the most striking anatomical feature being a heavy skeleton and weak musculature. This is especially marked in the hind legs. The body weight and skeletal age are not a function of the degree of postmaturity nor of the sex of the calf. This contradicts earlier statements concerning postterm weight gain.2 Animals less than 2 weeks postmature may be heavier and have larger skeletons than animals that are 6 or 7 weeks postmature. The condition is not sex linked. It is our impression that the female calf is weaker than the male calf at delivery and presents a more difficult problem when salvage is attempted.

The postmature Holstein-Friesian calf is characterized further by a complete absence of the suckling reflex, lack of the gag reflex, and an inability to clear the upper respiratory passages of amniotic fluid and mucus. There is an apparent lack of hunger sensation and a lack of vocalization except during the first postnatal day. Previous reports6, 7 emphasized the abnormally low level of blood hexoses at delivery and a rapid decline of the blood hexose beginning at delivery and terminating 6 or 8 hours later in hypoglycemia. The metabolic state of the animal is not improved measurably with intravenous infusions of glucose.6 The body temperature, normally 101° F., may fall as low as 93° within 2 hours. Shivering is prominent. If there is no intervention, the animal passes into shock and dies in hypoglycemic coma within 6 or 8 hours.

Since the first reports on the postmature Holstein-Friesian calves, additional cases have been studied. Studies on postmature pregnancy in the Holstein-Friesian breed have centered on attempts at fetal salvage, and this has been done because of the premise of genetic conditioning of gestation length and the possible role of the metabolically defective homozygous recessive fetus and its placental component in the parturient process. If such a fetus were to survive and were to prove fertile, mating of this animal to proved heterozygotes would increase gene frequency in the experimental herd, provide an adequate test of the genetic premise, and should provide more cases of abnormal gestation for study.

In recent studies on postmaturity in the Holstein-Friesian breed, we have accumulated pertinent biochemical and clinical data in 5 postmature calves delivered by cesarean section and treated with hydrocortisone immediately after presentation. Two normal term calves delivered by cesarean section have been used as controls. The major findings to be reported here are the adrenal insufficiency in all postmature calves and severe thyrotoxicosis in 3 of the 5 with a lesser hyperthyroidism in the 2 remaining cases.

Methods

The diagnosis of postmaturity in the 3 bull and 2 heifer calves described below was made on the basis of known insemination date of the cows, the known heterozygosity of the bull and 4 of the cows for the gene in question, the pedigree of the fifth cow, and the lack of maternal preparation for parturition in all of the cows. Presumptive evidence was strengthened by the appearance and behavior of the newborn and the blood chemistry of the calves immediately after delivery.

All calves had the body conformation and characteristics of postmaturity described previously. Weak quadriceps muscles and a lack of gag, cough, swallowing, and suckling reflexes were noted in all cases. There were varying degrees of staining of the hair coat with meconium. Three of the 5 calves were severely stained. In 2 cases the amniotic fluid was olive green in color and was more concentrated than normal. In 2 cases, from

identical matings, the volume of amniotic fluid was in excess of normal. This was associated with a thick, parchment-like amnion.

At cesarean section the upper respiratory tract of the calves was manually drained of mucus and fluid. Blood was obtained by jugular venipuncture; penicillin and streptomycin were given prophylactically, and in 2 cases oxygen was administered. Terramycin and/or neomycin were fed as soon as feasible.

After the respiratory pattern improved, the animals were given drip infusions of hydrocortisone alcohol in 20 per cent glucose. Two hundred milligrams of the steroid was given over periods of 8 to 20 hours. All animals received 250 mg. of hydrocortisone acetate intramuscularly on the first and third days, and 50 mg. on the fourth day.

Except for Calf 409 all animals received colostrum. Because suckling and swallowing reflexes were absent, whole milk was fed by stomach tube at 6 hour intervals for the first 3 days and at 8 hour intervals for varying periods of time. Milk was supplemented with vitamin B complex at each feeding, and 200 mg. of neomycin was fed once per day.

In the cases described, the following methods were used: whole blood glucose was measured by the Folin-Malmros methods after modified Somogyi precipitation of the protein. Serum sodium and potassium were determined on a Coleman flame spectrophotometer. Chlorides were determined by Scribner's modification of the method of Schales and Schales.⁹ Serum proteins were determined by the biuret method,¹⁰ and plasma-free hydroxycorticosteroids (17-OH-CS) by the method of Peterson.¹¹ The San Mateo Medical Laboratories analyzed serum for protein-bound iodine (PBI).

In those cases where it was feasible to measure adrenal response to ACTH, 25 U.S.P. units of the lyophilized product was infused in Ringer's solution over a 6 hour period. Plasma analyses for 17-OH-CS were made at 2, 4, and 6 hours after the infusion started.

Calf 409. A brief description of this animal has been reported. It was a 108 pound bull and

was 45 days postmature. It received no colostrum and, hence, no maternal antibodies. Infections in the umbilical stump, the anterior chamber of the eye, and the joints of the legs were encountered over the first 6 weeks and were successfully controlled by erythromycin and chloramphenicol. Two hundred milliliters of bovine gamma globulin was given on the tenth and twelfth days.

On the twelfth day 25 U.S.P. units of ACTH was administered by drip over a 6 hour period, and the adrenal response was measured by estimating plasma 17-OH-CS.

During the first month, fasting hypoglycemia was marked; it ranged from 8 to 32 mg. per cent, but no clinical signs of shock were observed.

After 6 weeks the weight gain became normal. There were numerous episodes of extreme lethargy not usually associated with hypoglycemia. There were other episodes of hyperpyrexia and blowing respiration.

The animal was placed in pasture when he was 5 months old. Except for slow body movements, he appeared well. Beginning at the seventh month and at monthly intervals thereafter, semen was collected by electro-ejaculator. Sperm was first found at 8 months. After 11 months the animal was used for breeding. Libido was good. One cow conceived from breeding and subsequently bore a postmature calf. During this time there were periods when there was transient hypokalemia (3.1 mEq. per liter) and hypochloremia (99 mEq. per liter).

At 14 months the animal underwent a sudden collapse. Except for a slight weight loss there had been no abnormal clinical or biochemical findings prior to collapse which was associated with profound muscular weakness and tremor. The animal was alert. At this time the animal had a well-developed rumen, hence, fasting levels of glucose could not be determined. Serum sodium, potassium and chloride were within normal limits. On the supposition that this was a manifestation of adrenal insufficiency, 100 mg. of hydrocortisone hemisuccinate and 100 units of corticotropin were given. During the following days the animal had a normal rectal temperature and pulse. Rumen motility was depressed and the iris did not react to light. The position of the head, placed along the side of the thorax, was like that seen in hypocalcemia. Serum calcium (ionized) was 3.7 mg. per 100 ml. Attempts to elevate serum calcium with calcium gluconate were successful, but the serum potassium level declined to 2.3 mEq. per liter

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and chloride to 89 mEq. per liter despite slow venoclysis of KCl. Rectal temperature rose to 108°, respiration was blowing in nature, and heart sounds were metallic. Ice water drenches and spraying were effective in reducing the temperature. The animal died the following day. At necropsy, the right adrenal gland was found to weigh 45 grams, the left, 47 grams. This is in contrast to 15 gram weights for normal single glands. In addition, a 2 cm. cortical adenoma was found in the left adrenal gland.

Plasma obtained prior to steroid therapy and subsequently frozen was then analyzed for 17-OH-CS. Forty-three micrograms per 100 ml. of plasma was found.

Calf 410. This bull was 31 days post mature and weighed 120 pounds. Colostrum was fed when he was 2 hours old. No infections were encountered. All feeding was done by stomach tube because of the inability of the calf to swallow when the posterior pharynx was stimulated by fluid. Despite great vigor at delivery and less complicated postnatal history, this animal was extremely lethargic and moved only when stimulated during the first week. Thereafter there were episodes of dyspnea and tachycardia. There was no fever at any time. Fasting glucose ranged from 32 to 58 mg. per cent. There were no abnormalities in serum ions at any time. When the animal was 2 months old he collapsed and died within 4 hours. No terminal clinical or biochemical findings were available.

Calf 411. Calf 411 was a 29 days postmature heifer that weighed 85 pounds. She was weak at delivery and exhibited extreme muscle flaccidity. Despite the hydrocortisone-glucose infusion, she went into shock within 4 hours. This was associated with bradycardia, a weak pulse, a body temperature of 93°, and a blood glucose level of 16 mg. per 100 ml. Six hundred milliliters of maternal blood were given over 4 hours. On the next morning the animal became more alert, with increased muscle tone. It had a normal body temperature and walked around the pen. By afternoon there was tachycardia with a strong heart rebound. Rectal temperature was 106°. Respiration was noisy and blowing despite clear lungs and pharynx. The animal rested on the sternum, held its head high, and forcibly breathed through the open mouth. The eyes were staring. The calf was bathed in ice water. Fasting glucose was 16 mg. per 100 ml. The condition of the calf remained static during the next day. It died on the fourth day.

Calf 422. Calf 422 was a 39 days postmature heifer. It was the largest animal in this series, weighing 139 pounds. There was marked generalized asthenia and particularly poor muscle development and tone in the hind legs. This animal did not develop suckling, swallowing, gag, or cough reflexes throughout its life.

Immediately after receiving the first 500 ml. of 20 per cent glucose with 100 mg, of hydrocortisone it went into hypoglycemic convulsions. It responded to rapidly infused 50 per cent glucose. During the second infusion of glucosehydrocortisone, muscle activity improved; the animal lifted its head and became alert. Respiration was steady and quiet. Five hundred milliliters of maternal blood was infused. Frequent blood sampling indicated that the postprandial glucose was 45 mg. per 100 ml. and fasting glucose was 32 mg. per 100 ml.

On the second day the packed cell volume of the calf had dropped to 20 per cent and a second transfusion of maternal blood was given. Thereafter the animal began to show increased interest in standing and walking. The latter was hindered by the long hind legs and poor adduction. For the next 15 days the animal was exercised daily. Rectal temperature varied widely from normal. There was a steady loss of weight and episodes of hyperesthesia were common.

On the eighth day 25 units of ACTH was administered over 6 hours by drip infusion to test adrenal cortex function. Prior to the twentieth day, fasting levels of glucose became progressively lower and reached 13 mg. per 100 ml. on the nineteenth day.

On the twentieth day the animal became very hyperesthetic and extremely weak. Diarrhea was noted, the fecal mass being liquid and bile stained. One hundred milligrams of hydrocortisone was administered intramuscularly. Protein supplements, such as whole eggs and gelatin, and antidiarrhea agents did not change the fecal consistency.

Twenty milligrams of hydrocortisone was given each day for 4 days. Five grams of NaCl was given at each feeding. Improvement in the glycemic state was noted, but the animal became weaker and died on the twenty-fifth day.

Calf 424. Calf 424 was a 117 pound, 11 days postmature bull. In contrast to other animals in this series, it bawled vigorously at delivery. Treatment of this animal was identical to that used in Calf 409. The blood glucose, however, rose to 155 mg. per cent as a result of the in-

Table I. Blood picture of 5 postmature calves and 2 normal calves (all data obtained within 15 minutes of delivery)

	Normal	Normal	409	410	411	422	424
Hemoglobin (grams)	10.5	83	9.8	7.3	10.3	7.9	
Leukocytes (No. per c. mm.)	7,300	5,850	10,000	8,400	10,700	3,350	14,900
Eosinophils (No. per c. mm.)	286	44	358	429	286	286	77
Packed cell volume (%)	43	30	47	37	34	27	33
Total reducing substances							
(mg. per 100 ml.)	118	140	56	71	64	82	82
Fructose (mg. per 100 ml.)	82	122	31	56	57	72	68
Glucose (mg. per 100 ml.)	36	18	25	15	7	10	14
Nonprotein nitrogen (mg.							
per 100 ml.)	19.2	26	23.2	19.8		23	_
Na+ (mEq. per liter)	158	148	154	153	165	147	160
K ⁺ (mEq. per liter)	4.4	4.4	4.5	4.9	5.8	4.9	5.1
Cl (mEq. per liter)	105	103	103	108	110	88.4	99.2
HCO₀⁻ (mEq. per liter)	25.2	20.1	17.1	20.1		22.2	16.6
Ca (mg. per 100 ml.)	12.5	10.5	11.2	11.0		11.0	
P (mg. per 100 ml.)	9.6	9.7	9.7	9.3		14.8	-
Serum protein (grams per 100 ml.)	4.9	4.2	4.2	4.3	4.3	4.2	3.8
Icteric index (units)	5	5	5	5	5	5	5
17-OH-CS (µg per 100 ml.)	6.1	7.1	5.0	8.9		5.5	
Cholesterol (mg. per 100 ml.)	92		178	126	77	46	-
PBI	9.4	6.6	8.8	10.2	15.2	12.7	13.1

fusions. The clinical picture did not improve. The animal had rapid, noisy respirations, a heart beat that could be observed along the thoracic cage, and severe hyperesthesia. Insertion of the rectal thermometer or touching the animal on any part of the body caused extensive reaction.

On the second and third days, the animal, although very weak, had normal, quiet respirations and a normal pulse that became increasingly heavy. Fasting glucose was 32 and 21 mg. per cent. Serum chlorides were 97.5 mEq. per liter. Serum sodium was 138 mEq. per liter.

On the fourth day, the rectal temperature was 105°. The animal became restless, moving its head from side to side. The respiration was blowing with the animal's mouth open and the eyes staring. Metallic heart sounds were noted. The animal was packed in ice. Diluted cold milk was fed by stomach tube. Five grams of NaCl was fed with the milk.

Blood analysis at this time indicated fasting glucose of 26 mg. per 100 ml. and serum chloride of 98 mEq. per liter.

Throughout the next 2 days, ice packs, aspirin, and cold milk maintained the body temperature within normal limits. NaCl was given at each feeding, and Lugol's solution was fed once per day. On the seventh and eighth days the animal was treated as before, but was unable to stand.

On the ninth day adrenal response to ACTH was measured.

Thereafter episodes of hyperpyrexia, tachycardia, and blowing respiration occurred. Analysis of serum indicated that fed NaCl was not able to bring the animal to sodium and chloride balance, the sodium being 129 and chloride 97.5 mEq. per liter. Throughout the tenth day one liter of 1.5 per cent NaCl was administered by slow venoclysis. This was followed by two liters of 0.9 per cent NaCl. Oral administration of salt was maintained. Throughout this period heavy, labored respiration, tachycardia, and general uneasiness were noted.

By the fifteenth day hypostasis had resulted in lung consolidation, and the animal was killed.

Results

Blood analyses and hemograms obtained from postdelivery samples are given in Table I. Total reducing materials, i.e., glucose and fructose, were approximately the same as data presented previously. Serum and plasma were frozen for future reference. PBI analysis was not done until thyrotoxicosis was suspected in Calf 424. Since this syndrome had not been described in calves, we were not able to evaluate the clinical picture in the first cases.

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Results of the ACTH infusion in 2 normal and 3 postmature calves of the same postpartum age are shown in Fig. 1. These data indicate a severe adrenal insufficiency in the postmature calves when they are considered with the general metabolic picture.

Glucose. All animals had consistently low fasting blood glucose levels. The ranges in milligrams per 100 ml. were: Calf 409, 8 to 48; Calf 410, 29 to 56; Calf 411, 12 to 16; Calf 422, 13 to 47; and Calf 424, 17 to 37. Control calves of the same ages had fasting levels of glucose of 48 to 76 mg. per 100 ml. It is of interest that only Calf 422 had hypoglycemic convulsions, and then only in the first few hours of life. They occurred, however, immediately after infusion of 100 mg. of hydrocortisone in 20 per cent glucose.

Blood sugar levels measured 2 hours after feeding varied greatly. Maximum levels in each case were: Calf 409, 80; Calf 410, 88; Calf 411, 42; Calf 422, 63; and Calf 424, 80 mg. per 100 ml. This is in contrast to an average of 110 mg. per 100 ml. found in the control animals.

Serum ions. Serum sodium, potassium, chloride, and bicarbonate were within normal limits in Calves 410 and 411 throughout their lives. Calf 409 had normal serum ion concentrations during the first 6 months but had episodes of hypokalemia and hypochloremia thereafter. Calf 422 had persistent hypochloremia from birth the range being 88.4 to 105 mEq. per liter. Hyponatremia was not evident until the thirteenth day. Sodium fluctuated between 128 and 141 mEq. per liter with most sera having less than 135 mEq. per liter. Calf 424 had hypochloremia at delivery. Serum chloride levels never exceeded 103 mEq. per liter. Although the sodium concentration was normal at delivery, it declined progressively and after the seventh day was never higher than 134 mEq. per liter. In no instance was serum potassium increased above normal levels, i.e., 5.7 mEq. per liter.

The concentration of serum protein was normal in all cases. There were insufficient data on protein fractions to draw reliable conclusions.

Protein-bound iodine. The PBI in the serum of normal term calves at delivery ranges from 7.0 to 10.0 μg per 100 ml. In a representative normal animal the PBI was 10.0 μg per 100 ml. at delivery, 8.4 at 5 days, 6.5 at 9 days, 4.7 at 12 days, and 7.6 at 14 days. Except for Calves 409 and 410, the postmature calves had elevated PBI's at delivery and maintained high levels throughout their lives (Fig. 2).

At necropsy, the pituitary gland was seen to be smaller than in normal controls of the same age. There was marked degranulation of the acidophil cells.

In Calves 410, 411, 422, and 424 the adrenal cortex had minimal development of the zona glomerulosa and little, if any, differentiation of the zona fasciculata and reticularis. In fact, the zona glomerulosa could be considered to be embryonic. In Calf 409 an adenoma was found on one adrenal gland. Both glands were three times normal size. Associated with the adrenal changes was a plasma-free 17-OH-CS level of 43 µg per 100 ml.

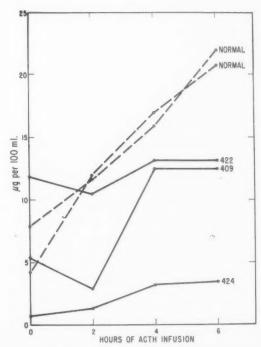


Fig. 1. Plasma 17-OH-CS of normal and postmature calves during infusion of 25 IU of ACTH.

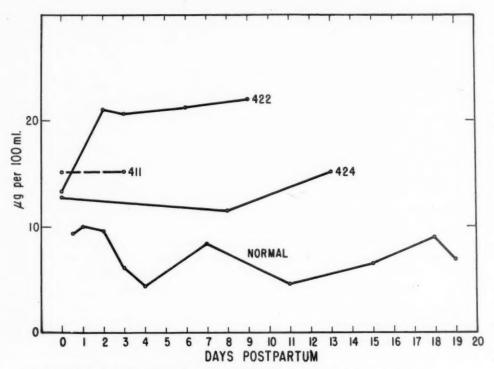


Fig. 2. Protein-bound iodine in serum of 1 normal and 3 postmature calves.

The detailed description of these and other endocrine organs will be reported separately.

Comment

The thyroid-adrenal relationship is well known¹²⁻¹⁸ from the standpoints of clinical and laboratory experimental investigations. Although the present study does not shed more information on this area, the postmature calves may present ideal subjects for further investigation of these relationships.

The syndrome described above would appear to have adrenal and thyroid components. All animals studied had persistent hypoglycemia which was especially marked during fasting. All animals went into shock within a few hours of delivery. Persistent hypochloremia was found in 2 cases, but hyponatremia occurred only after several days. In those animals surviving beyond the period of hydrocortisone therapy, the adrenal response to ACTH was less than that found in normal calves of the same age.

These findings, in addition to the presence of hypoplastic adrenal cortices found at necropsy indicate that the calves were adrenally insufficient, the Addisonian state corresponding to the crises described by Schwartz.¹⁹

Calf 409 which had hypoglycemic episodes during the monogastric phase of metabolism and transient hypokalemia and muscle weakness when he became a ruminant animal presented certain features at collapse that were similar to aldosteronism as described by Conn.²⁰ It is unfortunate that the plasma-free Porter-Silber chromogens (three times the normal concentration) were not characterized and that urine and/or plasma was not assayed for aldosterone.

Coexistent with the adrenal insufficiency or related causally to it were signs of hyperthyroidism in 3 of the animals (Calves 411, 422, and 424). Although Rupp and Paschkis²¹ describe the coexistence of Addison's disease and thyrotoxicosis, we believe that the data indicate that the hypermetabolic state of the

calves was a direct reflection of the very low adrenal activity. The hyperthyroid state was not evident for several days after delivery and was noted only after the cessation of adrenal steroid therapy. It is postulated that the decrease in adrenal steroid with time triggered the thyroid gland as described by Harris and Woods.18 The PBI levels in serum tend to confirm the clinical data and do so in those cases where the clinical data were most like that described for thyroid "storm."

The clinical and biochemical findings in the case of Calves 409 and 410, although incomplete from the standpoint of iodine determinations, are considered to reflect adrenal insufficiency essentially uncomplicated by a hypermetabolic state. This is substantiated to a large extent by the relative ease of maintaining the animals for extended periods of time.

These considerations lead to the proposition that postmature Holstein-Friesian calves have adrenal insufficiency, varying in degree and manifestation with the extreme insufficiency producing hyperthyroidism.

It is of interest and, we believe, of importance that this syndrome is genetically conditioned and occurs in the postmature Holstein-Friesian calf irrespective of gestational age.

The events in utero that lead to the disturbed metabolism are not known. Further study will be needed to determine the intrauterine events and the relation of these and the adrenally insufficient postmature calf to prolonged pregnancy and by inference to those events that determine normal parturient physiology.

Summary and conclusions

Five postmature Holstein-Friesian calves have been studied and compared with term

All postmature animals exhibited some degree of hypoadrenocorticism as measured by fasting blood sugar, serum ions, response to exogenous ACTH, and clinical and necropsy findings.

Those animals which had hypochloremia and hyponatremia in addition to a low fasting blood sugar showed signs of hyperthyroidism which correlated with elevated concentrations of serum PBI.

The adenohypophysis, smaller than normal and exhibiting degranulation of the acidophil cells, may be the prime defective organ, the hypoadrenalism resulting from inadequate or deranged drive by the pituitary gland.

Although the relationship between adrenal insufficiency of the fetus and the genetically conditioned prolonged gestation is unknown, the constancy of this relationship may provide a clue to the disturbed preparturient physiology of the cow.

We are indebted to the Upjohn Company for supplies of ACTH, Cortef, and Solu-Cortef.

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Growth and development

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X. Feeding practices with Negro infants 6 to 8 weeks old and their relationship to various maternal factors

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ALTHOUGH the principles and the practical application of infant nutrition are more or less firmly established, innovations and trends in infant feeding have become evident in recent years. The extent of breast feeding, in particular, has claimed the attention of various investigators who have noted a decline of this practice in our culture.1-3 The decrease in the incidence of breast feeding has led investigators to believe this tendency to be unrelated entirely to the ability or inability of mothers to nurse the infant. Instead, the influence of such maternal factors as age, parity, socioeconomic status, education, and pre- and postnatal nutrition is being emphasized in this area. Accordingly, the incidence and duration of breast feeding as related to maternal factors is the topic of numerous reports in the literature. Studies by Williams,4 Robinson,⁵ and Salber⁶ revealed that age had no influence on breast feeding. Similarly, Norval⁷ reported that "... age of the mother did not affect the duration of breast feeding, once it had become established." On the other hand, Jackson⁸ found that "age, education, and color were shown to be related to duration of breast feeding, older mothers, better educated mothers and Negro mothers nursing longer." Lussky⁹ observed that the incidence of breast feeding decreased with age.

More consistent findings were noted among investigators when education and socioeconomic status of the mother were related to incidence and duration of breast feeding. In a review of current trends in the feeding of infants, Smith¹⁰ stated that ". . . the practice of breast feeding is nowadays more likely to be directly related to the mother's education . . . than to maternal poverty and ignorance." According to Salber,6 "The most important factors contributing to a higher percentage of breast feeding were college education of the mother and higher social class." Likewise, Westropp¹¹ found that "Social and economic conditions have a pronounced effect on breast feeding habits."

Included among current trends in infant feeding is the practice of adding solid foods to the infant's diet at a relatively early age. Butler and Wolman¹² conducted a survey on "Trends in the Early Feeding of Supplemental Foods to Infants." Replies from 2,000 questionnaires revealed that a majority of the doctors introduced supplemental foods to the normal infant's diet at either 2 to 4 weeks (30 per cent) or 4 to 6

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This investigation was supported by Research Grant No. RG-3761 (CE) from the National Institutes of Health, United States Public Health Services. weeks (32 per cent). In the "Symposium on Trends Elicited by the Survey," Anderson¹³ linked early supplementation with the decline in breast feeding. He stated that "The progressive decline in the number of breast-fed babies . . . is perhaps another contributing factor to the insistence on the part of the mother that solid foods be begun early."

The wide divergence in opinions and practices regarding the most advantageous age to introduce solid foods is fully recognized. The benefits, if any, that are derived from early supplementation of the infant's diet is the point at issue. In recent studies by Sackett14 and Crews,15 solid foods were introduced to infants as early as 2 to 3 days after birth. Despite the usual criticism of such a schedule, both investigators enumerated several advantages from this early introduction of solid foods. Glazier16 compared the physical and nutritional development of infants receiving solid foods early (2 to 3 months) with infants receiving solid foods at a later age (4 to 10 months). His results indicated that the most advantageous age to begin solid foods was during the second and third months of infancy. On the other hand, Deisher¹⁷ compared the physical progress of infants who were given solid foods during the first 4 weeks of life with that of infants receiving solid foods between 9 and 12 weeks. He reported that "Growth between the two groups was comparable . . . " as were the other factors investigated. The Committee on Nutrition of the American Academy of Pediatrics, 18 recognizing the need for some specific recommendation regarding the most favorable time for introducing solid foods, recommended that ". . . no nutritional superiority or psychologic benefits results from introduction of solid foods into the infant diet prior to 21/2-3 months of age."

The purpose of this paper is twofold: first, to present the feeding practices adopted for 388 Negro infants and, second, to examine the relationship between age, parity, education, socioeconomic status, and the pre- and postnatal diet of the mother, and

the findings pertaining to the infant. This study is part of a larger project, designed to examine the anatomic, physiologic, and psychological factors influencing the growth and development of Negro infants. One phase of the nutrition aspect of this major study, previously reported, is the "Relationship Between Prenatal Maternal Nutrition and Socio-economic Index, Weight of Mother and Birth Weight of Infant." 19

Method and materials

Breast feeding is not fully established until the mother's milk supply is available, generally between the third and fifth postpartum days. This is usually the time when mother and infant are being discharged from the hospital. Since the mode of infant feeding has not been definitely established at this time, it would seem reasonable to investigate infant feeding practices at some subsequent period. For this reason, 6 to 8 weeks after birth of the infant was chosen for the period of study. Due to various circumstances, however, some mothers were interviewed outside these limits. Approximately 80 per cent of the mothers were seen during the prescribed time. Among the remaining one fifth, none were seen earlier than at 4 weeks or later than at 10 weeks. The average age of the infants at the time of interview was 51 days.

The mothers considered herein were also seen during the antenatal period. Subsequent contact with these mothers, during the postpartum period, furnishes the materials for this report.

A detailed account of the infant's feeding pattern prior to and at the time of inquiry was ascertained during the interview which included information on the following items:

1. Type of feeding: method of feeding the infant at the time of interview, classified as (a) breast-fed, (b) breast-fed with milk supplement, or (c) artificially fed.

2. Breast feeding practices: method of infant feeding prior to the time of inquiry, namely, (a) breast feeding never attempted, (b) breast feeding attempted, but discontinued, or (c) breast feeding continued.

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3. Duration of breast feeding: length of time that baby was breast-fed.

4. Expectation of weaning: when mother planned to discontinue breast feeding.

5. Kind of formula: construction of formula, type of milk used, and total amount of formula taken daily by the infant.

6. Supplements included: additions to the milk feeding, including vitamins, oleum percomorphum, orange juice, and solid foods. The age at which the supplements were introduced was asked.

Postnatal nutrition. The maternal diet during the postnatal period was examined at this time. Each mother whose infant is included in these analyses was questioned concerning her eating habits during this period. In addition, she was instructed to either record all foods eaten for a 3 day period or to recall all foods ingested during the 24 hour interval just prior to the time of interview. A complete description of the procedures used in collecting and analyzing these records, which is the same as that used for prenatal records, appears in a previous paper. 19 Each dietary intake was then classified as lactating or normal, dependent upon whether the mother was breast feeding (with or without milk supplement) or artificially feeding the infant. Finally, the nutrient intake levels of these records were compared with applicable nutrient allowances as recommended by the National Research Council²⁰ to determine the adequacy of the intake of this group of mothers. Accordingly, a scale with a range of from 10 (very poor) to 50 (excellent) was used to evaluate each nutrient intake, the total of which comprises the final rating of the dietary record.

Medicosocial data. Information pertaining to the mother's medical history, which included age and parity, was taken from the hospital record after delivery. Data relative to socioeconomic status and education of the mother were collected by the medical social worker through interviews during the prenatal period. The socioeconomic classification referred to herein consists of four groups, from I (low) to IV (high), and is

described in detail by Crump and associates²¹ in the first report of this "Growth and Development" series.

Results

Type of feeding. When the infants were classified into three groups according to type of feeding at the time of interview, it was shown that 69.1 per cent of the infants were not breast-fed, while 16.5 per cent were breast-fed only, and 14.4 per cent breast-fed with milk supplement.

Upon closer examination, however, it was noted that over one third of the infants in the "no breast feeding" group were breastfed for a period prior to the time of investigation. A somewhat higher percentage of the infants (55.7 per cent) would therefore appear in the breast feeding groups if one considered data for these infants obtained at age 3 to 4 days after birth. Meyers² conducted a survey in 1956 to determine the extent of breast feeding in the United States. His reports from the Southeastern region of the country revealed that 27 per cent of the infants were discharged from the nursery on breast, 16 per cent on breast and bottle, and 57 per cent on bottle only. A further breakdown revealed that Tennessee (with less than one half of the hospitals included) reported 44 per cent of the infants on breast, 18 per cent on breast and bottle, and 38 per cent on bottle only. It will be noted that the percentage of infants in the breast feeding groups in our study is lower than that reported for Tennessee but slightly higher than the average for the Southeastern region of the country (Fig. 1).

Breast feeding practices. Three categories are used to describe the infants according to breast feeding practices: (1) breast feeding never attempted (44.3 per cent), (2) breast feeding attempted, but stopped (24.7 per cent), and (3) breast feeding continued (30.9 per cent). Of the total number of infants who were breast-fed for some period, over one third (35.1 per cent) of the infants were breast-fed for one month or less, and 44.4 per cent for 2 months or less. Ravenholt,²² in a similar study, obtained a feeding his-

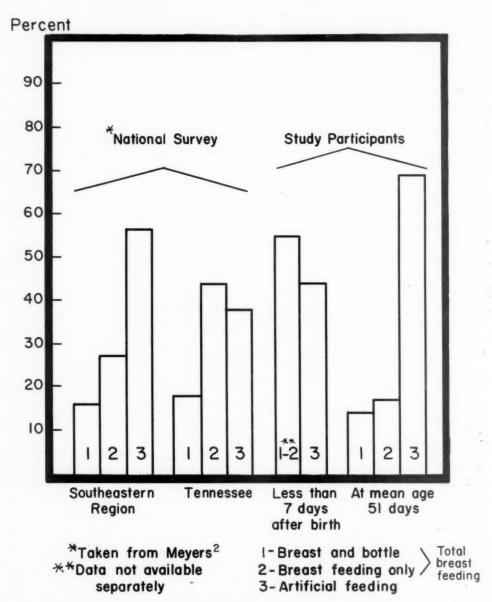


Fig. 1. Comparison of type of feeding of newborn infants for the Southeastern region, Tennessee, and Nashville Negro mothers (in percentages).

tory from 709 mothers during the second postpartum month. This survey revealed that "... 40 per cent had tried to nurse their babies, but at the time of inquiry... only 17 per cent were still nursing." In each instance, the number of mothers who had stopped breast feeding at the time of inquiry represented over one third of the group who had attempted breast feeding.

Thus, these results tend to agree with the conclusion postulated by Anderson³ that "... one third to one half of the mothers who do attempt breast feeding discontinue doing so in one month or less..."

Duration of breast feeding. Breast feeding was not attempted with 44.3 per cent of the infants included in this study. The length of time breast feeding was continued for the

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remaining infants varied from 1 or 2 days to 8 weeks or more. Therefore, average duration of breast feeding could not be established for the entire group inasmuch as 30.9 per cent of the infants were still being maintained on the breast with or without complementary feeding. It was possible to determine duration of breast feeding, however, for the infants who were no longer being breast-fed when mothers were contacted. The mean duration of breast feeding was 17.1 days and the median, 13.9 days.

Expectation of weaning. The expected time of weaning reported by the mothers, in most instances, was based on previous per-

formance with other children, plans to resume regular employment, or the decrease in flow of milk. The expected time of weaning for the infants who were still being breast-fed at the time of interview ranged from around 3 months to 15 months, with 43 per cent of the mothers planning to wean around 3 months. Sixteen per cent of the mothers could give no definite time when they expected to wean their infant, although most of these mothers felt that weaning would take place at some point after 3 months. Only 3.7 per cent of those mothers who were definite expected to breast-feed beyond 9 months.

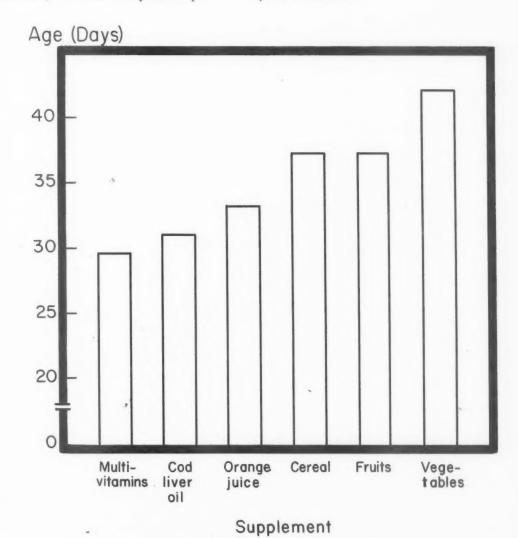


Fig. 2. Mean age of infant when supplemental feeding was begun.

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Table I. Comparative statistics on the age, education, and parity of mother, by type of feeding

	Ag	e of mot	her	Educa	tion of r	nother		Parity	
Type of feeding	AF*	BF†	Com.‡	AF	BF	Com.	AF	BF	Com.
Mean	25.1	25.8	25.0	10.7	10.7	10.2	1.8	2.1	1.8
Standard deviation	5.9	5.8	5.8	2.6	2.2	2.9	2.0	2.1	1.8
Median	23.7	24.4	24.9	11.1	11.3	9.9	2.8	2.1	1.8
N	268	64	56	253	62	56	268	64	56

*Artificial feeding.

†Breast feeding.

Combined (artificial and breast) feeding.

Table II. Comparative statistics on the age, education, and parity of mother, by breast feeding practices

	Age of mother			Educa	tion of me	other	Parity		
Breast feeding practices	Stopped	Contin- uing	None	Stopped	Contin- uing	None	Stopped	Contin- uing	None
Mean	26.0	25.4	24.6	10.2	10.5	11.0	1.7	2.0	1.9
Standard deviation	6.4	5.8	5.5	2.6	2.4	2.5	1.6	2.0	2.2
Median	24.6	24.4	23.3	9.4	10.9	11.6	1.8	2.0	1.7
N	96	120	172	90	118	163	96	120	172

Vitamin supplementation. It is generally agreed that the normal infant can be maintained adequately for the first 3 months of life on human milk or a properly constructed cow's milk formula, provided that supplements of vitamins C and D are added as early as possible in the first months of life. Over two thirds (69 per cent) of these infants were receiving multivitamin supplements at the time of interview. The mean age at which vitamins were started was 29.7 days or 4.2 weeks (Fig. 2). An additional 5.2 per cent of the infants received vitamins A and D in the form of oleum percomorphum.

Orange juice was the source of vitamin C for 37.4 per cent of the infants. In most instances, when orange juice was given, multivitamin supplements were included. This was true for 71.7 per cent of that group.

Introduction of solid foods. It was observed that early supplementation of the infant's diet was not too common in this study. However, the addition of cereal in the infant's diet was reported by 30.4 per cent of the mothers, and strained fruits and vegetables by 10.1 and 6.2 per cent of the mothers.

ers, respectively. Cereal was introduced as early as the second week of life and as late as the eighth week, but the mean age was 37.2 days. Similarly, the mean age for the introduction of strained fruits was 37.2 days, and 42.1 days for strained vegetables.

Maternal factors and infant feeding practices

Maternal age and parity. Mean age of the mothers by type of feeding and breast feeding practices is shown in Tables I and II. No significant association is apparent. When mean age was considered in relation to breast feeding practices, however, it was noted that mothers who were breast feeding at the time of investigation and those who had discontinued were slightly older than the mothers who had never breastfed. Further analysis, with use of chi-square, failed to show any relationship between these factors.

Maternal age did not influence the expected time of weaning as reported by these mothers. Here again no significant relationship was noted between the two factors.

Neither the chi-square test nor analysis

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of differences in mean parity reveal any significant differences between parity of the mother according to (1) type of feeding and (2) breast feeding practices. There were fractional differences in mean parity but when rounded off to the nearest whole number no difference was noted (Table I).

Socioeconomic index. Only in the analysis regarding expectation of weaning was socioeconomic status related to infant feeding practices. The association, which indicated that mothers in the higher socioeconomic groups weaned earlier than mothers in the lower groups, was significant at the 2 per cent level of confidence. This relationship was indicated when a chi-square test was made with mothers dichotomized according to socioeconomic level* and with expectation of weaning categorized as shown in Table III, with one exception. The test excluded all mothers who had no definite expectation on weaning.

Education. Smith¹⁰ states that, "College graduates now hope to nurse their babies; 25 years ago poorer mothers expected to do so." The results of studies cited earlier tend to support this generalization, while findings in our study are directly opposite. The analvsis of differences in mean level of educational attainment, according to breast feeding practices, showed a higher level (eleventh grade) for mothers who never breast-fed their infants than for mothers who were still breast feeding (10.5) or those who had stopped (10.2) at the time of interview.

Maternal nutrition and infant feeding practices. An earlier study presents the prenatal dietary intake of these mothers.19 Differences in the pre- and postnatal ratings of the mothers are shown in Table IV. It will be noted that 28.5 per cent of the postnatal ratings are an improvement over the prenatal ratings, 35.4 per cent did not change, and 36.1 per cent were lower ratings. In most instances, there was no great degree of shifting in dietary ratings between the two periods of observation. Thus, a direct association between the pre- and postnatal ratings was found.

Prenatal nutrition showed no particular influence upon infant feeding practices. Chisquare test of association between prenatal dietary ratings and (1) type of feeding and (2) breast feeding practices failed to show any significant relationship between the attributes.

On the other hand, maternal postnatal nutrition was significantly related to type of feeding as well as breast feeding practices. The association in both instances was significant at the 0.1 per cent level. Mothers in the artificial feeding group had higher dietary ratings than those who were still breast feeding. No data are available to give reasons why these mothers did not practice breast feeding or why nursing was discontinued after a relatively short period. How-

Table III. Mothers' expectation of weaning by socioeconomic group (in percentages)

	Socioeconomic group							
Expectation of weaning	I (low)	II	III	IV (high)				
Unknown	-	19.4	9.8	25.0				
3 months or later	85.7	77.4	68.3	75.0				
Earlier than 3 months	14.3	3.2	22.0	_				
Total	100.0	100.0	100.0	100.0				
N	7	62	41	8				

Table IV. Differences in rating on prenatal and postnatal diet of mother (in percentages)

	Rating on prenatal diet								
Rating on postnatal diet	Very poor	Poor	Fair	Good	Excel- lent				
Excellent	-	.9	-	-	-				
Good	5.0	3.7	13.3	18.4	100.0				
Fair	21.2	25.0	33.3	42.1	-				
Poor	28.8	36.1	33.3	18.4	-				
Very poor	45.0	34.2	20.0	21.0	-				
Total	100.0	100.0	100.0	100.0	100.0				
N	80	108	75	38	1				

^{*}Socioeconomic Groups I and II and Groups III and IV were combined.

Table V. Mothers' expectation of weaning according to rating on postnatal diet (in percentages)

	Postnatal rating								
Expectation of weaning	Very poor	Poor	Fair	Good	Excel- lent				
Unknown	13.0	11.8	20.0	33.3	-				
3 months or later	67.4	79.4	80.0	66.7	-				
Earlier than 3 months	19.6	8.8	-	_	-				
Total	100.0	100.0	100.0	100.0	-				
N	40	30	20	3	-				

ever, it is fully recognized that factors other than the nutrient intake of the mother determine the mode of feeding the infant. Nevertheless, from a nutritional standpoint, the better nourished mothers are more able to breast feed than those poorly nourished. Ebbs²³ found an asociation between the postnatal diet and the incidence and duration of breast feeding, evidenced by a decrease in the percentage of breast-fed babies as the nutrient intake of the mothers became less adequate. As indicated, our findings failed to show this relationship.

No relationship is apparent between postnatal dietary ratings of the mothers and expectation of weaning (Table V). Of the mothers still breast feeding, however, only those with poor and very poor ratings appear in the earlier than 3 months category. It is logical then to expect those mothers with fair and good ratings to nurse longer, since, at this point, all mothers in these categories are concentrated in the 3 months or later and unknown groups.

Maternal factors and supplementation of infant's diet. The percentage of mothers supplementing the infant's diet, divided according to socioeconomic status and education of the mother, is shown in Table VI. With advancement in socioeconomic status and level of educational attainment, a steady increase will be noted, in most instances, in the percentage of mothers giving supplemental feeding. The most striking percentage differences, however, are between the highest and lowest categories of each maternal group. For example, 25.8 per cent of the mothers in socioeconomic Group IV (high) had introduced strained fruits into the infant's diet by the time of inquiry, whereas only 8.7 per cent of the mothers in Group I (low) had started fruits.

Further analysis indicating a positive relation between cereal introduction and socioeconomic status, was significant at the 2 per cent level of confidence. Similarly, a significant association (at the 0.1 per cent level) was shown between cereal supplementation and education of the mother. Several other differences between socioeconomic status, education of the mother. and supplemental feeding of the infant were not statistically significant but, nevertheless, were suggestive because of their consistency. There was a tendency among mothers in the higher socioeconomic and education groups to add multivitamin supplements earlier. Likewise, better educated mothers introduced orange juice earlier.

Table VI. Percentage of mothers employing supplementary feeding, by socioeconomic group and education of mother

Supplement	Socioeconomic group				Education of mother				
	I	II	III	IV	Less than 8th	8th grade	9th-12th grade	College 1-4	
Multiple vitamins	52.2	53.3	64.4	71.0	50.0	53.8	57.9	71.2	
Cereal	21.7	26.4	32.6	54.8	20.4	32.7	25.8	51.5	
Fruit	8.7	6.0	12.6	25.8	11.4	9.6	6.7	21.2	
Orange juice	39.1	33.0	43.7	32.2	34.1	34.6	36.8	42.4	
Vegetables	8.7	4.9	4.4	12.9	2.3	3.8	4.3	13.6	
Cod liver oil	13.0	5.5	5.2	0.0	6.8	3.8	5.7	4.5	
Total N	23	182	135	31	44	52	209	66	

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Summary

We have investigated infant feeding practices among 388 Negro mothers and the relationship of these practices to various maternal factors (age, parity, prenatal and postnatal nutrition, socioeconomic status, and education).

From the data presented, it was indicated that no great divergence in breast feeding practices was evident when this group was compared with similar studies appearing in the literature. For example, there were slight differences in the incidence of breast feeding among these mothers (55.7 per cent) as compared to averages typifying the Southeastern region of the country (43 per cent),2 and for Tennessee (62 per cent). Likewise, these findings are in agreement with Anderson's conclusion that, ". . . onethird to one-half of the mothers who do attempt breast feeding discontinue doing so in one month or less. . . ." More than one half of the infants were breast-fed for some period, but breast feeding had been stopped with 35.1 per cent in one month or less, and with 44.4 per cent in 2 months or less.

Further consideration of these data revealed that (1) of those mothers still breast feeding at the time of interview, 43 per cent planned to wean around 3 months, while only 3.7 per cent expected to breast

feed beyond 9 months; (2) an appreciable number (69 per cent) of the infants were receiving multivitamin supplements; and (3) the early addition of solid foods to the infant's diet was not practiced to any great degree by these mothers; 30.4 per cent of the infants were receiving cereal at the time of interview; 10.1 per cent, strained fruits; and 6.2 per cent, strained vegetables.

Finally, the role of various maternal factors in the management of infant feeding by this group of mothers was explored. Results of this investigation indicated that maternal age and parity as well as the prenatal diet showed no particular influence upon the feeding practices employed for these infants. It was found, however, that certain other maternal factors considered in this study were significantly related to the findings characterizing infant feeding practices. These relationships indicated that: (1) mothers in the higher socioeconomic groups weaned earlier than mothers in the lower groups; (2) with advancement in socioeconomic status and education of the mother, a steady increase was noted, in most instances, in the percentage of mothers employing supplemental feeding; (3) mothers in the artificial feeding group had higher postnatal dietary ratings than those who were still breast feeding.

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Fetal effects of radioactive iodine therapy in a pregnant woman with thyroid cancer

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RADIOIODINE therapy in millicurie dose ranges may be used in selected cases to inactivate functioning thyroidal metastasis.

It is known that I¹³¹ traverses the placenta and this has been documented in both animals and human subjects. Chapman and associates¹ have demonstrated that the fetal thyroid concentrates iodine after 14 weeks' gestation. Although the fetal thyroid weight at 3 months' or so gestation is unknown, a reasonable estimate would be only a few milligrams.²

This report may serve two functions; i.e., to show possible injurious effects of I^{131} on a fetus and eradication of functional cervical metastasis, follicular type, with systemic radiotherapy employing I^{131} .

A woman with functioning thyroidal cervical metastasis was treated with 77 mc. of I¹³¹ when 3 months pregnant. The doctors were unaware of the pregnancy. Russell and co-workers have reported 2 such cases; one child died at 2 months, 3 weeks of age with a respiratory infection and an anatomic diagnosis of "cretinism (treated)"; no demonstrable thyroid tissue was present at autopsy. The second child was apparently well at 4½ months and was on 90 mg. of thyroid extract daily.

From the Radioisotope Section and the Thyroid Clinic.

The contents of this article reflect the authors' personal views and should not be construed as a statement of official Air Force policy.

In the case to be presented the child is at present $2\frac{1}{2}$ years of age. The case with available laboratory data is as follows:

The mother, a gravida v, para ii, white woman, was a registered nurse. She was first seen when 37 years of age on Sept. 10, 1956, and had had a swelling on the left side of the neck for a period of over 12 months. In September, 1955, at another Air Force Base the patient experienced mild nervousness and a sensation of choking. A 3 by 0.5 cm. node in the left side of the neck was palpated at that time, and it was felt, clinically, that she had infectious mononucleosis. From November, 1955, through August, 1956, there was no change in this left neck mass, and the patient continued to be tired and nervous.

In September, 1956, at a civilian hospital, biopsy of the mass in the left side of the neck was accomplished with a resulting diagnosis of papillary adenocarcinoma, of mixed papillary and follicular type. When first seen by our staff on Sept. 10, 1956, the patient had an easily palpable nodule in the left lobe of the thyroid, some 2 cm. in diameter. In addition, she had an irregular mass some 2 inches in diameter in the left neck beneath the sternocleidomastoid muscle.

On Sept. 14, 1956, she had a total thyroidectomy and radical left neck dissection. At that time, evidence of gross tumor was present. A few days later the patient developed Horner's syndrome on the left side, which has persisted (Fig. 1).

Because of palpable nodes that appeared on the right side for the first time in November, 1956, a right neck dissection was arranged; however, it was not possible to intubate the patient at

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during operation, so the procedure had to be terminated.

At no time in her history has the patient ever demonstrated any bone or chest mestastases.

A few days before the operation, on Sept. 10, 1956, the 24 hour I¹³¹ uptake was 1.4 per cent. It was felt that some preoperative medication was blocking the uptake of I¹³¹ in the thyroid gland.

In January, 1957, some 4 months after the operation, uptake was 6.6 per cent in 24 hours. In an effort to induce maximum uptake, the patient was placed on methimazole, 10 mg. 3 times a day for 30 days. On Feb. 5, 1957, the uptake, after methimazole had been discontinued for 72 hours, was 7.5 per cent. The "rebound phenomenon" should have assured the maximum uptake at this time. A large tracer dose of 750 µc of I131 was given with 2 areas of activity delineated in the right side of the neck. One measured 5 by 7 cm., the other 1.5 by 2.5 cm. It is possible that the larger concentration of I131 may have represented a residual right lobe or capsule, but the smaller concentrate of activity superiorly and laterally located is clearly outside the usual confines of the normal thyroid and thus, ipso facto, represents functional thyroid metastasis (Fig. 2).

On Feb. 11, 1957, the patient received 77 mc. of I¹³¹ orally. In 10 days she was put back on thyroid extract as she was completely myxedematous.

On March 12, 1957, the patient announced, to our dismay, that she had not experienced any menstrual periods since Nov. 5, 1956. She had all of the signs and symptoms of pregnancy of approximately 4 to 5 months' duration, with an expected delivery date of Aug. 12, 1957. It was then ascertained that at approximately 3 months' gestation she had been given the therapy dose of I¹³¹.

It was felt by a majority of those concerned with the case that a therapeutic abortion should be performed. This was offered to the mother but she refused. On July 25, 1957, at 38 weeks, the patient was delivered of a premature child weighing $4\frac{1}{2}$ pounds.

On Oct. 2, 1957, a scintigram again showed function on the right side of the midline, and the patient was given an additional 73 mc. of I¹³¹

On Feb. 27, 1958, the patient had zero uptake after thyroid extract had been stopped for 5 weeks, and she was doing well. A scintigram

showed no residual activity in the neck. On July 22, 1958, 116.7 μ c of I¹³¹ was administered orally with 94 per cent urinary collection within 72 hours. This would be excellent evidence that there was no functioning thyroid tissue. A neck and mediastinal scintigram remained negative with no activity demonstrable.

The most recent information from the patient reveals that she is again pregnant, well, and on oral thyroid extract replacement therapy, with no evidence of recurrence of thyroid cancer.

The baby was born July 25, 1957, and spent 29 days in the hospital. Birth weight was 4 pounds, 8 ounces; he was 18 inches long. On Aug. 2, 1957, the protein-bound iodine level was 9.6 μg per cent at 8 days of age. The baby was gaining weight and appeared to be progressing satisfactorily. On Aug. 21, 1957, the 24 hour uptake of I¹³¹ was 3 per cent. This was not felt to be valid inasmuch as the baby regurgitated a considerable part of the dose shortly after administration. The baby was discharged from the hospital on Aug. 23, 1957, weighing 4 pounds, 12 ounces.

He was first seen as an outpatient on Sept. 3, 1957. His weight had increased to 5 pounds, 14



Fig. 1. Patient at 40 years of age following total thyroidectomy and radical left neck dissection.

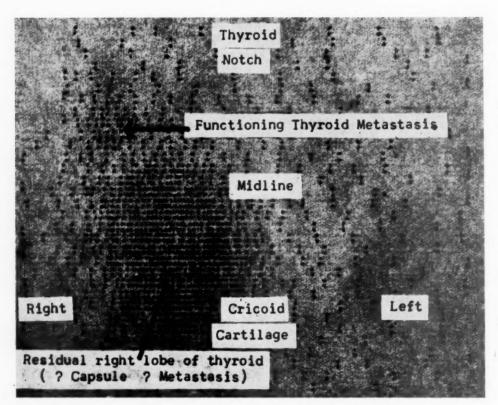


Fig. 2. Scintigram accomplished on Feb. 8, 1957, 3 days before 77 mc. of I131.

ounces, and except for the appearance of an umbilical hernia there was no change in his condition. The umbilical defect measured 0.5 cm. On Sept. 9, 1957, the baby's weight had increased to 6 pounds; the second PBI report from August 19 was 3.9 μg per cent. Blood was again drawn on September 9 for a third PBI determination. On September 27 the hernia was noted to have increased considerably in size, but the baby was making good progress otherwise.

On Oct. 15, 1957, the baby weighed 8 pounds, 2 ounces, his head circumference was 34 cm., chest 35 cm., and he was 53 cm. long. However, the child was noted to have a large tongue, and the umbilical hernia had increased in size. Skeletal x-ray studies at 83 days of age revealed the absence of distal femoral and proximal tibial epiphyses. The baby was started on oral thyroid extracts, 15 mg. daily, and oral iron because of a hemoglobin level of 9 Gm. per cent and a hematocrit determination of 27 (Fig. 3). The thyroid dosage was increased to 60 mg. daily over the next 2 weeks. The PBI level on Oct. 15, 1957, was 2.4.

On Dec. 18, 1957, the baby appeared to be making excellent progress. His weight had increased to 11½ pounds; he was alert, active, and healthy. The umbilical hernia had decreased in size. The PBI level was 8.0 and the hemoglobin, 11.5.

He was examined on Jan. 29, 1958, at which time psychometric measurements were performed. He appeared to be making excellent progress and was active and happy. The umbilical hernia had closed completely. The tongue was normal (Fig. 4).

Gesell and Amatruda developmental schedules were used in evaluation of the baby by psychiatric consultation. After considerable study, the child's behavior placed him at 26 to 28 weeks in terms of the Gesell and Amatruda scales. His vocalizations and his lack of ability to sit momentarily appeared slightly below his age level. However, in the motor sphere his attempt to grasp both cubes seemed slightly advanced for his age.

On Feb. 27, 1958, he was doing well. The PBI level was 9.7; thyroid extract was continued at 60 mg. daily. He was seen on May 19, 1958,

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and the mother reported that he had been well except for a fall the week before when he struck his head and was unconscious for 30 minutes. Skull x-ray findings appeared normal. Follow-

ing recovery of consciousness, he seemed to be

completely well. His progress was felt to be satisfactory.

On May 19, 1958, a PBI determination was 7.3. The baby was last seen on June 25, 1958, and was doing very well. He accompanied his parents to another air base and continued to progress satisfactorily until March, 1959, when, at 20 months of age, he started having repeated convulsive episodes (Fig. 5). In August, 1959, the mother was told by the attending physicians and psychologist that the child was retarded and showed extreme hyperactive behavior. He was placed on 30 mg. of phenobarbital three times a day. Later this was changed to hydroxyzine, 5 mg. four times a day, and 25 mg. diphenylhydantoin four times a day. It was the psychologist's opinion that the child's behavior indicated brain damage. He responded moderately well to a regime of anticonvulsants and tranquilizing medications.



Fig. 3. Baby at 83 days of age when oral thyroid extract was started Oct. 16, 1957. Note umbilical hernia.



Fig. 4. Baby at 203 days of age on Jan. 29, 1958.

Comment

It is estimated that the total body dose to the mother from the initial 77 mc. of I¹³¹ approximated 29 rads by use of the following calculations³:

Total dosage formula:

 $\begin{array}{cccc} \mathbf{D_{beta}} + \mathbf{_{gamma}} = & (73.8 \times \overline{\mathbf{E}_{beta}} + 0.0346 \times \overline{\mathbf{g}} \\ \times \mathbf{I_{gamma}} \times \mathbf{CT_{eff}}) \end{array}$

Symbols:

 $D_{beta} = Dose$ from beta particles $D_{gamma} = Dose$ from gamma radiation



Fig. 5. Appearance of child at 24 months of age.

Weight of patient = 60 kilograms Height of patient = 169 cm.

Toff = Effective half life (estimated at 1

E_{beta} = day)
= Average energy of beta particles = 0.187 Mev.

Igamma = I-Gamma = roentgens_per mc. hr. at 1.0 cm. distance

73.8 = Constant employed in beta particle

dosimetry
0.0346 = Constant employed in gamma ray

g dosimetry
= Geometrical factor for gamma ray
dosage calculations = 120

 $D_{\text{beta}} = 73.8 \times (0.187) \times 1 \times \frac{77,000}{60,000} = 17.6$

 $D_{gamma} = 0.0346 \times 2.18 \times 1 \times 120 \times \frac{77,000}{60,000}$ = 11.5 rads

Therefore:

D_{beta} + gamma = 29 rads

Calculation of the blood dose would re-

quire radioiodine blood levels which are not available. For an approximation of the blood dose, we have used calculations developed by Seidlin, Yalow, and Siegel⁵; usually the blood dose is about twice the total body exposure. We estimate the blood dose to the mother to have ranged in the vicinity of 1 rad per millicurie or 77 rads. The material blood dose is high inasmuch as the patient had minimal circulating thyroid hormone tagged with I¹³¹, which would have kept contributing to the thyroid dose after the first few days.

Any dose calculations regarding the radiation received by the fetus or fetal thyroid are speculative. We estimated the fetus to be at 3 months' gestation at the time of the therapeutic dose of I131. A minimal or an enormous dose might have been delivered. At birth the child had typical immature features but did not have the findings seen in cretinism such as coarse hair, constipation, dull face, thick tongue, dry skin, umbilical hernia, and apathetic appearance. Although we had no initial laboratory or clinical evidence of cretinism, at 21/2 months of age, the large tongue, umbilical hernia, retarded ossification centers, and depressed PBI determinations established the diagnosis of hypothyroidism; and the baby was placed on oral thyroid at 83 days of age.

Subsequent I¹³¹ uptake, neck scintigram, and urinary excretion studies have shown no functioning thyroid tissue present in the mother following a second therapy dose of I¹³¹; thus, the original purpose of the radio-iodine therapy has been accomplished.

In view of the long period of normal behavior and development of the child while on regular, daily doses of thyroid extract, the convulsive episodes, mental retardation, and hyperactive behavior are hard to assess. They may or may not relate to the I¹³¹ therapy.

Summary

I¹³¹ therapy is an established method of eradicating functioning thyroidal tissue. In the case presented, an expectant mother with functioning cervical thyroidal metas-

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tases was given 77 mc. of the drug when 3 months pregnant. A chemical PBI of the child at 8 days of age established the presence of circulating thyroid hormone. The baby was born prematurely, weighing 41/2 pounds. During the first 2 months after birth, no evidence of cretinism was present, but hypothyroidism subsequently developed and the child was placed on oral thyroid extract at 83 days of age. The child had been well and had been maintained on oral thyroid extract for 20 months but then developed repeated convulsions which are at present under good control with appropriate medication. The dose received by the fetal thyroid may have been very great or very little. Ascertainment of the pregnancy status in all women prior to I181 therapy is suggested.

We wish to acknowledge Dr. Edith H. Quimby's constructive criticism dealing with the dose calculations and the technical assistance of S/Sgt. Emmett Parker, Jr., and A/1C Chandler S. Cheek.

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A male infant with a uterus

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WHEN the Wolffian ducts form the testicular excretory ducts, the Müllerian structures usually regress. One aberration in this usual sequence results in the rarest of the anomalies of the genital structures, a uterus in a male.

Case report

The mother was a 38-year-old white woman, gravida ii, para i, whose first pregnancy terminated in an abortion at 3 months' gestation. The mother was in excellent health; blood Group O, Rh-positive and Hinton-negative. The pregnancy was uneventful except for a second degree prolapse during the third trimester. On the second day after the expected date of confinement, the membranes ruptured spontaneously, and after 41/2 hours of labor a male infant was delivered spontaneously in the vertex position. The baby was noted to have multiple congenital anomalies, his condition at birth was poor and attempts at breathing were erratic. No resuscitative measures were employed, and the child was pronounced dead 10 minutes after birth.

At autopsy, performed 2 days post mortem, the child weighed 1,580 grams and measured 27 cm. crown-rump. The small bowel, liver, spleen, stomach, and a portion of large bowel were contained in a 3 cm. thin-walled sac which replaced most of the supra-abdominal wall. The heart contained two interventricular septal defects with a bicuspid pulmonic valve. The lungs were expanded. In the abdomen, the omphalocele noted on external examination contained a malrotated bowel with numerous fibrous peritoneal adhesions. The gall bladder was

hypoplastic; no extrahepatic biliary ducts could be identified, and there was prominent hepatic bile stasis. There was bilateral hydronephrosis with muscular hypertrophy of the bladder wall. No urethral obstruction was demonstrable. The adrenals appeared normal. There was an angiomatous vascular malformation over the medulla, temporal lobes, and Sylvian fissure of the brain.

The most striking finding was noted on examination of the pelvic organs. Lying between the bladder and the rectum was a small uterus with rudimentary Fallopian tubes coursing posteriorly around the normal rectum. The external genitals of the infant were those of an apparently normal male, the testes were descended in a normal appearing scrotum and the vas deferens, epididymis, and prostate appeared normal.

The placenta weighed 660 grams, measured 20 by 21 by 4 cm., and had but one umbilical artery in the cord. Microscopically the placenta was moderately immature.

Microscopic examination of the lungs, heart, liver, gall bladder, spleen, bowel, kidneys, and brain confirmed the gross impression. The adrenals were normal except for congestion of the central portion of the fetal zone. The bladder wall was hypertrophied but otherwise normal.

A cross section of the penis was normal and in sections of the prostate there were slightly dilated glandular spaces embedded in the usual stroma and filled with epithelial debris. The testicles were composed of immature tubules with abundant interstitial cells. No abnormalities were evident. The epididymis and vas deferens had the usual appearance.

On microscopic examination of the structure thought grossly to be a uterus, the typical features of an immature uterus were found (Figs. 1 and 2). The serosa was composed of low

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Present address: Department of Pathology Medical College of Virginia, Richmond, Virginia. cuboidal cells and beneath it were interlacing smooth muscle fibers. There was a central cavity lined by ciliated columnar epithelium and a few branching tubular glands. There were two lumina in the fundal portion of the organ but they fused to form a single cavity at a lower level. The Fallopian tubes were not sectioned.

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In normal development the Müllerian or paramesonephric duct appears at about the 10 mm. stage (at a time when the mesonephric duct is fully formed), courses caudad from a lateral cranial position, and fuses with its fellow in the midline. In the male, at about the 27 mm. stage, the Müllerian ducts lose their connections with the celomic cavity and begin to degenerate. The most cranial portion of the duct forms the appendix testis and the remainder disappears except for occasional small segments which may persist as embryonic rests. These rests, however, do not continue to differentiate and persist as simple tubular structures.

In lower forms of life, particularly insects, the morphologic sex is dependent on the sex-determining chromosomes, and if one part of the body is of a different genetic sex than the other, each side develops accordingly and a gynandromorph results.1 In mammals, however, the problem is much more complex and a large number of morphologic possibilities exist. While the development of the mammalian urogenital system is usually consistent with the chromosomal sex and follows the normal embryogenesis outlined above, the chromosomal determinants can be overwhelmed by hormonal factors and produce various abnormalities in the urogenital system. The classical example of this is the freemartin described by Lillie² in 1917 in which the female of unlike sexed bovine twins becomes masculinized when there are placental vessel anastomoses between its placenta and that of its male twin.

Jost,³⁻⁵ performed intrauterine castration of fetal rabbits at successive stages of development beginning at a stage when the testes could be recognized histologically but the genital tract had not begun to differ-

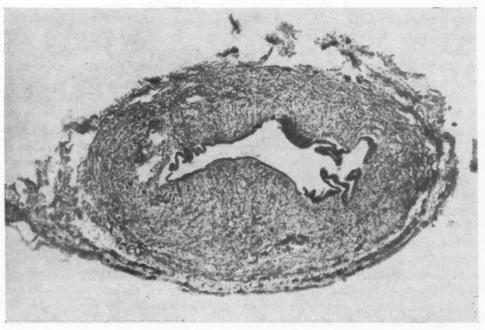


Fig. 1. Low-power view of uterus at a point after fusion of the Müllerian ducts. (Hematoxylin and eosin. ×40.)

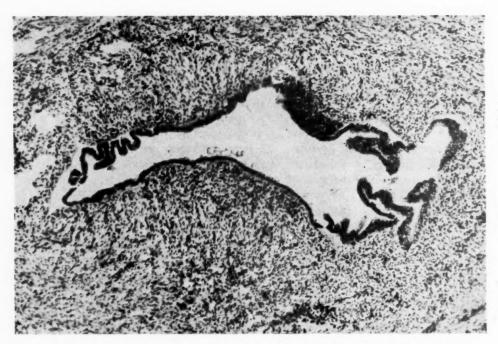


Fig. 2. Higher power view of Fig. 1 showing irregular, branching lumen lined by columnar epithelium and surrounded by smooth muscle. (Hematoxylin and eosin. ×100.)

entiate. He found, in the females, that organogenesis proceeded in a normal fashion but that, in castrated males, female genitals were produced. In the animals castrated progressively later after genital differentiation had begun, there was progressively less feminization until castration no longer had any effect on genital development. Furthermore, by unilaterally castrating the animals, Jost obtained unilateral feminization of the fetuses, suggesting that the testes exert their influence locally over a short distance. Wells and Fralick⁶ confirmed these observations in the rat. This demonstration of the tendency of the genital ducts to differentiate in a female direction unless influenced by the testis was extended by Jost and Bozic7 and Wolff and Haffen⁸ who explanted Wolffian and Müllerian ducts in vitro in a hormone-free environment and found that the Müllerian structures differentiated while the Wolffian ducts atrophied.

In the case presented in this communication the infant was of male nuclear sex by the method of Barr and associates⁹ and the male reproductive tract was normal histologically, including the testes. The structure of the uterus corresponds to that of approximately a 5 months' fetus. It would appear that in our case either the Müllerian ducts were not acted upon by testicular products (possibly due to late testicular differentiation or function or temporary cessation of function) or that they were not responsive to them, at least over a short period of time. It is probable, from the experiments of Jost and others cited above, that the testes were functional, at least at the critical period of Wolffian differentiation, since the Wolffian derivatives were well formed and the Müllerian derivatives were arrested at an earlier stage. The coexistence of multiple congenital anomalies with anomalies of the genitourinary tract and one umbilical artery has been discussed elsewhere in the literature. 10, 11

In the previously reported cases of a uterus in a male most were not strictly analogous to the present case. They were present in patients with multiple genital abnormalities, most frequently pseudohermaphroditism. Three very similar cases have

been reported, however, by Young, 12 Prichard, 13 and Gray. 14 In Prichard's and Gray's cases the uteri were found incidentally at operation in adults with no other genital anomalies. Young's case was that of a child with a vagina, uterus, and tubes as well as undescended testes, vas deferens, and a large phallus. In Gray's case the testes resembled histologically those of Klinefelter's syndrome, suggesting that, even though the

patient was male by the nuclear chromatin method, there was an underlying genetic defect which, while it usually lacks expressivity until adulthood, may act in utero.

Summary

A case of a uterus in a newborn male is described. The pertinent embryology is considered and a brief review of the literature is presented.

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Encephalocele attached to the placenta

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In spite of the fact that the problem of embryopathy evokes great interest, it is difficult to explain many congenital anomalies. This is understandable since the causes, exogenous and endogenous, are numerous, and their detection through anamnesis or retrospective investigations is often impossible. An important group of defects is composed of congenital disturbances of the umbilical cord, 11, 13 which can lead to underdevelopment of the fetus on the basis of anoxia or through a mechanical activity. 1, 2, 6-8 The following case may illustrate the latter mechanism.

The patient, a 26-year-old office clerk, came to the clinic complaining that she was 32 days overdue, without signs of labor. Family histories of both the patient and her husband were negative with regard to congenital defects.

The patient enjoyed good health. Her menses had always been regular. During the whole pregnancy she felt well and was under constant care of an obstetrician. Her living conditions were good and she had no domestic animals.

The fetus was found to be in breech presentation and there was no evidence of polyhydramnios. The next day labor began spontaneously and the patient was delivered of a live male infant, weighing 3,900 grams, whose head was attached to the placenta. There were a number of congenital defects. The umbilical cord, 24 cm. long, was fused distally with a soft, bluish, walnut-sized tumor which protruded from the forehead just above the right eye and was thought to represent rudimentary encephalic tissue covered by meninges. Beneath the tumor there was an oval defect in the cranium, measur-

ing 6 by 4.5 cm. The placenta, which measured 21 by 16 by 2.5 cm. and appeared to be well developed, was adherent to the encephalocele (Figs. 1, 2, and 3).

These anomalies are similar to those in two cases described by St. Hilare⁴ and Bagiński, Fijałkowski, and Kozłowski.¹

The maxilla and mandible, as well as the ears, were well developed. The medial nose cartilage protruded, the left nostril being normal, the right one split for a distance of 0.5 cm. On the left side of the nasal epiphysis there was a fold of skin 3 cm. long. The eyeballs were well developed, the right one being covered with eyelids. The left eyeball protruded and its conjunctiva was hyperemic; the lower eyelid was underdeveloped and the upper eyelid was unformed. The back of the head was covered by a rudimentary occipital bone, skin, and hair. The trunk and the extremities were normally developed. The muscles of the extremities were hypertonic. The sucking reflex was normal. The baby cried loudly and had a rhythmic heart beat of 80 per minute. Its breathing was shallow and irregular.

In order to ascertain the course of the placental vessels, 16 ml. of a 45 per cent solution of Pelviranum* was injected into the umbilical vein. X-ray did not reveal any connection between the placental vessels and the fetus in the spot where they were joined together (Fig. 4).

The state of the newborn, which was good at the beginning, gradually deteriorated, and death ensued after 47 hours.

An autopsy was performed by the Department of Pathologic Anatomy of the Medical Academy in Wrocław. It showed the left temporal bone to be displaced backward with a 5.0 by 4.2 cm. defect in the frontal bone. The left eye orbit

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^{*}Aqueous solution of diethanolamine salts of 3, 5 diiodide-4-pyridine-N-acetic acid, Warszawskie Zaklady Farmaceutyczne, Poland.



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Fig. 2.



Fig. 3.

was shallow, the occipital bone badly developed. Through this foramen a part of the frontal lobe of the left cerebral hemisphere protruded; it was covered with dura and pia mater. Just behind the foramen the meninges connected with the placenta. A badly developed skull cavity contained a very small quantity of brown tissue of jelly-like consistency, closely connected with the placenta through the foramen in the frontal bone. The texture of this tissue was in some places similar to cerebral tissue. Except for undescended testes, the other organs were within normal limits.

Histological preparations from the junction of the meninges with the placenta showed areas of focal necrosis in the placenta adjacent to other areas endowed with a good blood supply and islets of brain tissue. In some sections a typical cerebellar texture was noted (Figs. 5 and 6). Microscopic studies of the remaining organs did not reveal any fundamental deviations from the norm.

Histopathologic investigations performed in the II Clinic of Obstetrics and Women's Dis-



Fig. 4. State after injection of contrast medium (Pelviranum) into the vessels of the placenta. No connection between the placental circulation and the circulation in the fetus.

eases, Medical Academy in Wrocław, showed that there were foci of mononuclear leukocytes, with condensation of the glial tissue and calcification (Fig. 7).

The mother's blood type was B, Rh positive, the father's was O, Rh positive, and the baby's was B, Rh positive. Complement fixation tests for the toxoplasmic antigen in a 1:5 dilution were performed on the patient three times during the next 5 months and all were negative, as was the same text of the baby's serum. The Sabin-Feldman test was also negative. The patient did not permit a spinal tap. A Wassermann test was negative, as were chest x-rays of the mother and father. A hysterogram performed 5 months after the date of delivery showed no uterine abnormality.

In determining the cause of the abovedescribed congenital anomalies, the following possibilities should be taken into account:

- 1. Toxoplasmosis.
- 2. Formation of an encephalocele which adhered to the placenta.
- A too short umbilical cord might have forced the head of the fetus into proximity with the placenta.

Evidence for the toxoplasmosis theory are the calcified areas in the cerebral tissue of the fetus, for they are to a certain extent characteristic of this disease. Yet they were found in only one of the microscopic sections. Against this theory are the repeatedly negative serological reactions, as well as the fact that the fetus was mature and born alive, whereas in cases of toxoplasmosis the fetus is usually premature and stillborn. 5, 9, 10

As for the second theory, i.e., the formation of an encephalocele and its consequent merging with the fetal part of the placenta, the following observations should be taken into consideration: In case of such a hernia or anencephaly the result is usually either acrania or hemicrania; we very seldom see an asymmetrical loss of one or two bones of the skull. Then too, anencephalic fetuses



Fig. 5. Glia tissue with a focus of chorionic tissue (×40.)

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usually have a typical facial expression, of the so-called cretinoid type, which we did not observe in this case.

The third possibility, that of the short umbilical cord, seems a far more likely explanation. It seems logical that such a short umbilical cord might force the fetus to lie with its head pressed against the fetal surface of the placenta. The frontal bone, adherent to the insertion of the umbilical cord, would be subject to constant pressure, resulting in atrophy of the skin and frontal bone. There is, of course, other evidence in the literature of the destructive effects of the umbilical cord. Credé has described a case of a repeated twisting of the umbilical cord around the neck of the fetus resulting in its thinning to the diameter of a finger.12 Landau cited another case in which the head was parted from the trunk.12 Less striking examples of



Fig. 6. The placental tissue is directly connected with the glia tissue. (×40.)

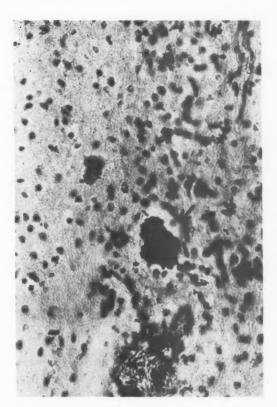


Fig. 7. Glia tissue with calcifications similar to those in toxoplasmosis. (×88.)

deformities of the extremities and atrophy of the muscles have been cited by Ebeler,2 Hennig⁶, Hörder,⁷ Kaboth,⁸ and others.

There are also numerous reservations to this theory. First of all, with respect to the forced position of the fetus, it is difficult to admit that under normal space conditions of the uterine cavity, even in the second half of pregnancy, the fetus could not take an oblique or transverse position. The abnormal development of the encephalon and of the cranial bones proves that the pathogenic factors were working at an earlier period of development. Thus, the etiology is not clear and it may involve two factors, viz., simultaneous developmental disturbances of both the umbilical cord and the cranium.

Addendum. Seventeen months later the described patient gave birth to a healthy baby, born at term without malformations, weighing 3,950 grams. Meanwhile the patient was not subjected to any prophylactic therapy.

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Bilateral theca lutein cysts associated with an apparently normal pregnancy

Case report

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IT IS common knowledge that bilateral theca lutein cysts are found in association with hydatidiform mole and choriocarcinoma. The occurrence of these cysts in normal pregnancies, however, is apparently quite rare. Three cases have been reported in association with hydrops or erythroblastosis, 1, 3, 5, 2 with twin pregnancies, 2, 6 and one with a normal single gestation. 4 We are reporting an additional case complicating an apparently normal pregnancy.

S. F. (201182), a 21-year-old Negro woman, para 1-0-0-0, was admitted to the U.S. Naval Hospital at St. Albans on Dec. 18, 1958. She complained of cessation of menses, intermittent low abdominal pain, and abdominal enlargement. Her last menstrual period was Sept. 20, 1958. She had noted lower abdominal discomfort for the 3 weeks prior to admission and during that same time she had also noted progressive lower abdominal enlargement. Past history, except for one questionable episode of salpingitis one year previously, was negative. Pelvic examination at that time was reported as normal. She had been seen by her family physician a week prior to admission and a biologic pregnancy test at that time had been reported positive.

Physical examination on admission revealed a well-developed, thin Negro woman in no acute distress. Abdominal palpation revealed a large mass in the left flank extending to the hypochrondium. A suprapubic mass extending almost to the umbilicus in the midline was also noted. Pelvic examination revealed the cervix to be pushed well up under and behind the symphysis pubis by a large cystic mass filling the cul-desac. The cervix was cyanotic and closed, and there was no bleeding present. The remainder of the physical examination was negative.

Preoperative work-up included a retrograde femoral arteriogram which demonstrated placental sinusoids in the suprapubic mass. A bioassay of chorionic gonadotropins was reported as 183 I.U. per milliliter of serum (normal at this stage of gestation). Complete blood count, urinalysis, and chest x-ray were normal, and the Rh type was positive.

Because of the marked abdominal enlargement and the pelvic and lower abdominal pain, on Dec. 23, 1958, an exploratory laparotomy was performed. The uterus was found in the midline enlarged to the size of a 12 weeks' gestation. The ovaries were bilaterally and symmetrically enlarged to approximately 15 by 20 cm. (Fig. 1). Grossly, they were multilocular and resembled theca lutein cysts. The left cystic ovary was high in the abdomen and the right was in the cul-de-sac.

Grossly there was no evidence of malignancy and the size of the uterus was consistent with the length of gestation. There was no abnormal elevation of the chorionic gonadotropins, no vaginal bleeding, and no evidence of toxemia. The retrograde femoral arteriogram had revealed what appeared to be normal placental sinusoids. It is of interest to note that, subsequent to this case, we had a case of proved hydatidiform mole

This article is not to be construed as necessarily reflecting the views of the Department of the Navy.



Fig. 1. View of bilateral cystic ovaries at time of first laparotomy.

on which a retrograde femoral arteriogram was reported as showing normal placental sinusoids. For the above reasons, it was felt that the diagnosis of hydatidiform mole was unlikely and that if a mole were present it could best be managed from below. The cystic ovaries and uterus were replaced and the abdomen closed.

On Jan. 5, 1959, the patient fell into spontaneous labor and aborted a macerated but otherwise normal fetus of the expected size. The placenta was also macerated but grossly showed no cystic change. On Jan. 13, 1959, there was acute torsion and rupture of the right ovarian cyst. At operation a right oophorectomy was performed. The left cystic ovary was found to be markedly reduced in size (6 by 8 cm.) Several of the larger cysts from this ovary were resected and the remaining ovarian tissue left in place.

Pathologically, cut sections of the removed ovary and of the cysts from the left ovary were typical of hyperreactioluteinalis. There was luteinization of both the theca and the granulosa cell elements (Fig. 2). The removed ovary contained hemorrhages into some of the cysts and rupture at the site of torsion. Multiple histologic sections of the placenta were normal and showed no evidence of hydatidiform mole or hydropic degeneration.

Grossly the fetus weighed 54 grams and its crown-rump length was 9 cm. The skin was severely macerated and there were two traumatic injuries evident. The right scapulohumeral joint was separated and the abdominal wall had a 2 cm. perforation. These injuries were sustained

because of the decomposition. No sections were taken of the fetus.

The patient was re-examined on Feb. 24, 1959. At that time the left ovary was palpably normal and chorionic gonadotropin titers were zero. She had a normal menstrual period March 15 to 19, 1959. On April 5, heavy, intermittent vaginal bleeding began, associated with low abdominal cramps and passage of clots. Flow ceased on April 15. Pelvic examination on April 17, 1959, revealed the uterus to be enlarged to the size of a 6 weeks' pregnancy and the left ovary to be cystic and enlarged to 8 to 10 cm. The rat ovarian hyperemia test was positive and chorionic gonadotropins were reported 41.1 I.U. per milliliter of serum. The ovary and uterus rapidly regressed in size thereafter and on June 16, 1959, they were normal on pelvic examination. Chorionic gonadotropins could not be demonstrated in the serum on that date. Subsequent menses have been normal and a premenstrual endometrial biopsy was reported as secretory on July 28, 1959.

Summary

A case has been presented of bilateral theca lutein cysts with an otherwise normal pregnancy. The purpose of this presentation is not to discuss or defend the management of this situation but rather to present an apparently very uncommon condition. It is interesting to note the recurrence of a left ovarian cyst when the patient apparently conceived and aborted again.



Fig. 2. Histologic section of cyst wall showing typical picture of hyperreatioluteinalis.

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Diabetes insipidus and pregnancy

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DIABETES insipidus is a rare disease characterized by a relative deficiency of antidiuretic hormone (ADH) with concomitant disturbances in water balance. The pathologic changes underlying the condition are destructive lesions of variable nature located in the hypophyseodiencephalic system.1 Among a series of 65 cases reported by Thomas2 one third were due to intracranial tumor, one third were of unknown etiology, and the remainder were ascribed to various granulomas and inflammatory lesions. The patient with diabetes insipidus because of deficient production of ADH has a marked reduction of renal facultative reabsorption of water and as a result polyuria, polydypsia, and urine of low osmolar concentration.

Various case reports and reviews of the literature have described variable effects of pregnancy when superimposed upon diabetes insipidus.³⁻¹⁰ Unfortunately, many of these patients were studied before the advent of precise procedures for definitive diagnosis of the condition and the reports may include cases of chronic renal disease, adrenal hyperfunction, and psychogenic polydypsia. The latter was impossible to differentiate from true diabetes insipidus before the availability of the Carter-Robbins test.¹¹ In general, pregnancy has been described as worsening, ameliorating, and effecting no change in diabetes insipidus.

Two recent well-documented reports have shown marked increases in vasopressin requirements during pregnancy. One dealt with diabetes insipidus following hypophysectomy.12 This patient had large urine volumes despite increasing doses of exogenous vasopressin throughout the third trimester of pregnancy but improved after delivery. It is of interest that she received a 75 mg. maintenance dosage of cortisone with much higher doses on occasion. The second report dealt with a patient13 whose vasopressin requirements increased during pregnancy and late in each menstrual cycle and decreased while nursing. Similar improvement while nursing has been previously reported.14

There are interesting ramifications of the combination of diabetes insipidus and pregnancy other than changes in antidiuretic function. Oxytocin production has not been assayed in patients with diabetes insipidus but sites of production and storage as well as release of oxytocin and ADH secondary to electrical and physiologic stimulation are markedly similar. For this reason, labor and delivery might be expected to be pathologic.

We have recently had the opportunity to observe and study 2 patients with proved diabetes insipidus during pregnancy, parturition, and the puerperium:

Case 1. E. K., a 34-year-old white womanpara 5-0-0-5, had suddenly developed excessive thirst and polyuria of approximately 9 liters per day in November, 1957. She was admitted to the University of Nebraska Hospital that month

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where the Carter-Robbins test confirmed a diagnosis of diabetes insipidus. Skull x-rays, visual fields, spinal fluid, fasting blood sugar, I131, PBI, and BMR determinations were all normal. There was no known diabetes insipidus in her family. She was started on intranasal vasopressin but soon changed to 1 c.c. (5 units) vasopressin tannate in oil every other day and was maintained on this dosage throughout pregnancy without significant change in intake and output. Total weight gain in pregnancy was 33 pounds.

There was spontaneous rupture of the membranes at 11:00 P.M. on March 31, 1959. (The estimated date of confinement was March 22.) After a 16 hour latent period contractions started on April 1. She had a first stage of 2 hours and 15 minutes, a second stage of 8 minutes, and a third stage of 13 minutes. She was delivered of a 2,755 gram infant spontaneously at 5:23 P.M., and the uterus contracted well after delivery of the placenta.

She had received 4 units of vasopressin tannate in oil (5 units per cubic centimeter) on the morning of delivery. Increased thirst was noted on the first postpartum day and 4 units was given daily until the sixth postpartum day when by noon the thirst and polyuria had abated and she returned to her normal schedule. She noted mild breast engorgement on the fourth postpartum day but this lasted only 24 hours. There was no spontaneous discharge of milk. Breast engorgement and "afterpains" were less than in any previous pregnancy.

On April 11, 10 days after delivery, there was no discernible breast engorgement and the only milk discharge had been 3 drops from the right breast on April 8. She was given 2 units of oxytocin intravenously and rapidly ejected about 25 drops of milk from each breast.

She was readmitted on May 28, 1959, when a Carter-Robbins test again confirmed diabetes insipidus (done after 72 hours without vasopressin tannate in oil). Since delivery, menstrual periods have been normal and she has remained on vasopressin tannate in oil, 1 c.c. every other day with daily intakes of about 2.5 liters.

Case 2. N. P., a 29-year-old white para 4-0-0-4, dated the onset of excessive thirst to Nov. 20, 1958, which she remembered as 17 days prior to the onset of her last normal menstrual period. This thirst and polyuria increased for 3 weeks and then stabilized around 7 liters intake and 5 liters output daily. Diagnosis of diabetes insipidus was established in the third month of gestation by a Carter-Robbins test. The patient kept her intake and output at pretreatment levels and only increased the frequency of dosage when these levels were exceeded. The dosage of vasopressin tannate in oil was increased gradually from 0.5 c.c. every 7 to 8 days in February to every 2 days in June, the sixth month of gestation. She maintained this level until time of delivery. The pregnancy was uneventful except for irregular spotting during the first 5 months. Total weight gain was 30 pounds. The estimated date of confinement was Sept. 14, 1959. On October 1, she began to have irregular contractions at 5:00 A.M. and was admitted at 8:00 A.M. She had hypertonic dysfunctional labor without progress for 19 hours. She was given morphine and had 6 hours rest but then (6:00 A.M., October 2) regular weak contractions began, continuing every 8 to 10 minutes for 7 hours with no significant progress. At 1:00 P.M. the membranes were ruptured artificially, contractions became hard, of 5 minute frequency, and at 2:00 P.M. she was delivered of a term infant without difficulty. The second stage was 5 minutes, the third 13 minutes. The uterus contracted well and blood loss was minimal. No oxytocics were given.

She had some breast engorgement and nursed the baby but stated she had less milk and "afterpains" than ever before. She stopped nursing the fourth week because milk output was poor and the baby failed to gain satisfactorily until supplementation was initiated. (She had nursed each of

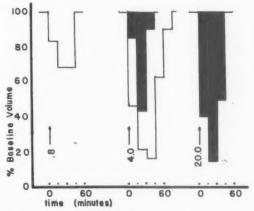


Fig. 1. Reduction of baseline urine output in Patient 2 after intravenous administration of vasopressin in milliunits as indicated. Values for thirty-sixth week of pregnancy are shaded; others obtained 9 weeks post partum. Baseline volumes 130 ml. (prepartum) and 140 ml. (postpartum).

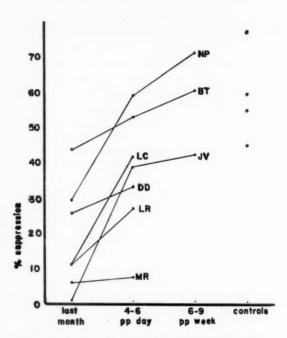


Fig. 2. Baseline urinary volume suppression—average (in per cent) for three 15 minute periods following intravenous administration of 4 mU. of vasopressin (except Patient B. T. who received 8 mU.) given at times shown in pregnant women and in nonpregnant controls. Solid lines connect points of a specific patient.

the previous infants successfully for 3 months.) Water exchange was about the same for the first 4 postpartum days and then showed a 20 per cent reduction that lasted until the tenth postpartum day. Since that time she has returned to the vasopressin tannate in oil dosage of early pregnancy (0.5 c.c. every 7 days).

Because of conflicting reports as to the effect of pregnancy on diabetes insipidus, we undertook to study the relative sensitivity of pregnant and nonpregnant women to vasopressin.

Method

Healthy, near term pregnant women from the obstetric clinic of the University of Nebraska Hospital were studied after 8 hours of dehydration. After an initial dose of 400 ml. of water by mouth, they were given 200 ml. each 15 minutes and urinary output measured until a stable rate of diuresis was obtained. After attaining this state of "physiological diabetes insipidus," they were given carefully measured intravenous injections of commercial vasopressin (all from the same lot) and the degree and duration of anti-diuresis noted. Similar experiments were done in the early and/or late postpartum period using proportional water load calculated on the basis of weight change. In some instances the effect of nursing was studied. Finally, similar experiments were done on nonpregnant patients and on the patients with diabetes insipidus. The latter were studied after 72 hours of deprivation of vasopressin tannate in oil.

The studies were analyzed as a quantal response and considered positive if a 25 per cent decrease in urine volume occurred for two 15 minute periods following administration of the vasopressin. A typical response is shown in Fig. 1.

The data obtained from the individualized studies were categorized for analysis (Table I and Fig. 2).

Results

It is obvious that observed activity of vasopressin is greater after delivery than during late pregnancy and is greatest in the nonpregnant state. From our studies we cannot be sure whether the decreased activity in pregnancy is due to (a) increased rate of deactivation, (b) decreased sensitivity of the renal tubules, or (c) increased glomerular filtration rate. Our few observations on nursing seem to bear out the antidiuretic effects as noted by Cross¹⁶ in rabbits and Kalliala¹⁷ in women, but Patient N. P. gave no response.

The 2 patients with diabetes insipidus appear variable in their clinical course.

In Case 1, no real change was noted in vasopressin tannate in oil requirements during pregnancy but the patient did require increased amounts for the first few days after delivery and then returned to the normal status. Labor and delivery were normal and rapid but rupture of the membranes preceded onset of labor. "Afterpains" and breast engorgement were less than in any previous pregnancy.

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In Case 2, progressive increase was noted in vasopressin tannate in oil requirement from the time of diagnosis in the third month of pregnancy until the sixth month, after which it remained constant until delivery. After delivery she returned to the requirements of early pregnancy. Labor was nonprogressive until after rupture of the membranes when it became very rapid and was followed by a short second and third stage.

Both clinical and experimental diabetes insipidus may be of variable severity or "completeness," and this is not surprising in view of the numerous etiologies of the syndrome, each with its own natural history and course. Brown and Rynearson18 reported patients with urine concentration to specific gravities of 1.011 and 1.016 with water deprivation. Kourilsky¹⁹ distinguished a category of patients with "partial diabetes insipidus" with urine concentration above 1.010. Cates and Garrod²⁰ have shown that 1 or 2 mg. of nicotine (or even inhalation of a cigarette) could cause antidiuresis in some patients with diabetes insipidus by stimulation of ADH release. Our patients (both nonsmokers) had a long period of antidiuresis after inhaling one or two cigarettes (Fig. 3).

Most reported cases either have become worse or have shown little change during

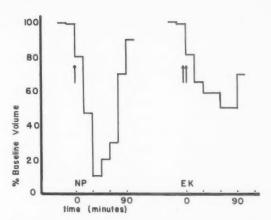


Fig. 3. Change in baseline output in 2 patients with diabetes insipidus following inhalation of cigarettes as indicated. One arrow represents one cigarette.

pregnancy. Other patients have had pregnancies with little change and then have become worse or better in a subsequent pregnancy, which suggests a change in the basic disease process rather than an effect of pregnancy. A few patients have shown improvement the last few weeks of pregnancy only to get worse for the first few days after delivery. This course of terminal improvement has been attributed to the fetal neurohypophysis, and certainly this gland contains ADH after the fourth month, but actual release of significant amounts by the fetus has not been shown. Nursing seems to bene-

Table I. Response to indicated doses of vasopressin (milliunits) by intravenous routes*

Patient	Age	Sex	Last month of pregnancy		4-6 days post partum		6-9 weeks post partum		Not pregnant	
M. R.	27	F.	.8-	4-	.8-	4-				
D.D.	16	F.	-8.	4-	-8.	4+	•			
J. V.	32	F.	-8-	4-	.8-	. 4+				+4
L. C.	21	F.	.8-	4-	.8-	4+				
B. T.	24	F.	-8.	8+	8-	8+	-8.	8+		
A.S.	24	F.	.8-	4-						
L.R.	27	F.	.8-	4-	.8-	4+				
N. P.	(P	t. 2)		4-		4+	.8+	4+		
F. L.	42	F.								4+
R. J.	32	M.							.8+	4+
B. S.	26	F.							.8-	4+
J. W.	29	M.							-	4+

^{*}A positive response indicates a 25 per cent decrease in urine volume for at least two 15 minute periods after administration of the vasopressin. All patients were normal except N. P. who had diabetes insipidus,

fit polyuria and a few cases, especially those with onset during pregnancy, have disappeared completely in the postpartum periods.

It is truly difficult to understand how any patient should improve in pregnancy. Robinson²² has shown that plasma levels of ADS* in the normal woman are elevated during pregnancy and further acutely elevated during the act of nursing. As our studies show, the response of pregnant women to exogenous vasopressin is decreased. This may be due to an increased rate of deactivation or a change in renal sensitivity. A vasopressin inactivating substance with enzyme-like characteristics has been demonstrated in the plasma of pregnant women23-25 as well as in placental extracts.26 Nevertheless, these studies involved incubation of the plasma for 1 to 24 hours with inactivation of the octapeptide which has a half life (at least in the rat²⁷) of approximately one minute, and it is difficult to evaluate the role of this "enzyme" in total body economy. Unfortunately, no ADH disappearance curves in pregnant and nonpregnant women are available for comparison.

If pregnancy causes elevated adrenal and thyroid hormone levels, these should intensify diabetes insipidus. Plasma 17-hydroxycorticoids are elevated during the latter half of pregnancy but it has also been shown that these patients have elevated levels of cortisol-binding protein and it may be that biologically active levels of hydroxycorticoids are the same as in the nonpregnant state. It is difficult to assay thyroid function during pregnancy. Though protein-bound iodine (PBI) levels may be increased it has been shown that estrogen will increase the PBI level in an athyrotic patient receiving constant replacement therapy,28 suggesting increased PBI may not mean increased rate of thyroxin liberation by the thyroid. Butanol extractable iodine levels are in the upper normal range29 and neither gives a key to activity at a cellular level.

A situation with both increased blood levels and increased inactivation rate could be maintained only by an increased rate of ADH secretion, while failure of normal pregnant women to manifest a reduction in water intake and output with elevated blood levels of ADS suggests a decrease in renal tubule sensitivity or an increase in water delivery to the distal tubule secondary to the elevated glomerular filtration rate of pregnancy. Whatever may be the stimulus for the increased ADH secretion rate, it seems reasonable that the pregnant patient with diabetes insipidus, even though she may have an incomplete lesion and respond partially, would not increase secretion to the degree that a normal patient would and would become relatively worse during pregnancy. This has been the case in most welldocumented reports and in our Case 2. If this result be less than dramatic it could, however, be masked by excessive amounts of vasopressin tannate in oil. We feel this may be so in Case 1. On the other hand, if nursing further stimulates ADH release in the patient with "partial" diabetes insipidus during a period of increasing sensitivity to vasopressin, she may require less or even no exogenous hormone.

Experimentally, bilateral interruption of the supraoptic-hypophysial tract has been followed by diabetes insipidus, clear-cut dystocia, and death during labor in cats and guinea pigs, attributed to lack of oxytocin. Among reports of diabetes insipidus in women one patient has been observed to have two prolonged labors with light contractions and finally spontaneous delivery of a dead fetus. This woman had one successful delivery following Pituitrin stimulation. No other reported cases indicate clear-cut uterine failure in labor.

Our second patient had 26 hours of labor without progress only to be delivered in one hour after rupture of the membranes. Her previous two labors were 3 to 4 hours in duration. The role of endogenous oxytocin in labor remains in dispute but we are inclined to believe, for many reasons, that it plays a part in normal parturition.

^{*}ADS, total antidiuretic activity of plasma. This is attributed to vasopressin or a like substance. Slope of the bioassay curve is parallel to commercial vasopressin.

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It seems reasonable that a patient with diabetes insipidus, particularly if incomplete, could still release oxytocin, since sites of storage (and synthesis?) of the two octapeptides, though confined to the general area of the hypothalamus and neurohypophysis, do show relative spatial differences.21 At any rate, fairly normal labor and delivery without postpartum atony is the rule in this disorder. It appears that oxytocin release, while it may be decreased to some degree, will be satisfactory for delivery, particularly if rupture of the membranes is effected.

Summary

1. The clinical course of 2 patients with diabetes insipidus in pregnancy has been presented. One required increased administration of vasopressin for stable water exchange, one was maintained on the prepregnancy dosage. In both delivery was effected and oxytocics were not required for or after delivery of the placenta.

2. The antidiuretic activity of exogenous vasopressin was shown to be decreased in pregnancy with increase after delivery.

3. Possible influences of pregnancy on diabetes insipidus are discussed.

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Melanoma and pregnancy

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THIS report is being made because in a limited obstetric practice in 27 years of approximately 1,000 cases, I have seen 2 cases of pregnancy and melanoma. In one, the melanoma accompanied the pregnancy and in the other, a florid recrudescence of a previous melanoma followed the pregnancy. In a discussion of Hendricks' case report,1 Coppedge stated that Cosgrove reports an incidence of 1 in 122,000 pregnancies. Search of the literature of the past 15 years reveals very few case reports in which pregnancy and melanoma are associated. With 2 exceptions a series could not be found and in only one instance² has one person had a personal experience with more than 4. The effects of melanoma with pregnancy or the effects of pregnancy on melanoma are variable and there is considerable disagreement.

Malignant melanoma, one of the least curable of all tumors, comprises about 1.3 per cent of all cancers in all age groups with an incidence of 2.2 per 100,000 male population and 2.6 per 100,000 female population.³ About 80 to 90 per cent of the melanomas arise in the skin. Hadley⁴ stated that malignant melanoma under age 30 is rare and in association with pregnancy rarer still. In my cases, one patient was 29 years old and the other was 34 years old.

Byrd and McGanity⁵ feel that pregnancy is a stimulating factor in the development and growth of malignant melanoma. The young woman who has had a malignant melanoma should be advised of the grave risk of pregnancy in that it may produce recrudescence of the tumor and appreciably shorten her life span. This risk is felt to be great enough to justify surgical sterilization

in those women who are amenable to terminating their child bearing career. Termination of the pregnancy before apparent spread has taken place may prevent or delay such a spread.5 Once the trigger has been pulled and metastases are present there seems to be little value in premature interruption of the pregnancy. Stewart⁶ also raises the question about terminating a pregnancy in a known case of malignant melanoma. Yet Allen reports an instance in which there was a spontaneous regression after pregnancy and in a 12 year follow-up the patient was well after the primary excision.7 He felt that the sequence of events strongly suggested that the metastases developed as a direct response to the stimulus of pregnancy and that they were in fact so dependent on this stimulus that upon its withdrawal they themselves disappeared. Pack and Sharnagel² stated that the transformation of benign nevi to malignant melanoma, the rapidity of their growth, their early dissemination, and the low rate of curability during pregnancy has not been generally known, largely because the personal experience of any one physician with this uncommon cancer has been too infrequent to project this fact upon his consciousness. Of their 32 patients, 14 or nearly 50 per cent were dead in 3 years or less. Pituitary, adrenal, and gonadal hormones stimulate change of benign nevi into malignant melanoma as evidenced by their growth and dissemination during puberty and pregnancy. Recently Pack⁸ stated that apparently the pregnant woman has two to three times the tendency to develop melanoma as the nonpregnant woman, making due allowances for comparative time spent

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as pregnant or nonpregnant. This fact serves to emphasize the great importance of the examination of pigmented moles in young women at the time of pregnancy and the re-

moval of moles showing any suspicious signs

of growth during this period.

In contrast to the above material, White9 in a very exhaustive study in California observed that all reports mentioning pregnancy indicated that pregnancy was a distinct threat to survival in women with melanoma. However, no report calculated actual survival statistics on a group of pregnant women, and none compared survival of pregnant women with that of nonpregnant women of the same age. Therefore, it was apparent that the statements in the literature regarding the deleterious effect of pregnancy on the course of melanoma were based on case reports and not on adequate statistical study. In his discussion, White felt that the present data on survival in women aged 21 to 40, who make up the group of women exposed to the greatest risk of pregnancy, do not contain large enough numbers of women to allow any conclusions regarding the effect of pregnancy on the course of melanoma. In his review of Stanford Hospital series and the California Tumor Registry, 5 and 60, respectively, some pregnant women with melanoma did well, but most did badly, dying with metastatic melanoma within a short period. Some nonpregnant women did well, with long survival; a few nonpregnant women died rapidly of metastatic melanoma. In the literature, however, there are repeated statements that pregnancy has a profoundly deleterious effect on the course of melanoma. Pack and Sharnagel² have the only series of any considerable size, and in their 32 cases of melanoma they do not calculate 5 year survivals or compare survival of pregnant women with that of nonpregnant women of the same age. Therefore, although one is tempted to accept their conclusions, because of their great experience with the disease and a literature that supports them, published data seem inadequate as a basis for any firm conclusion about the effect of pregnancy on survival of melanoma. Pack and Sharnagel noted that interruption of pregnancy did not improve survival of women pregnant during the course of melanoma. There have been, however, several reports of "spontaneous" (3, including Allen's) regressions of melanoma, usually of short duration, after delivery of a baby in pregnant women with melanoma.¹⁰⁻¹¹

It is interesting that White9 is not in agreement with Kinsey and Smith about the degree of malignancy of melanoma. He felt that the data presented and those of many others do not bear out the statement frequently made that melanoma is the most malignant of all tumors in humans. With the shortcomings of statistics on 5 year survival previously mentioned, the average⁹ 5 year survival of melanoma of 23 per cent in males and 34 per cent in females make the prognosis in melanoma far better than that in carcinoma of the stomach or lung, which are more common tumors and for which the 5 year survival for either sex is certainly less than 10 per cent.

Case reports

Case 1. This 29-year-old patient was first seen May 25, 1951, as a gravida ii, para i. She was delivered on July 20, 1951, and had an uneventful course. Unknown to me, she had a biopsy of the skin from the back on Oct. 11, 1951. The lesion was reported as malignant melanoma. On April 15, 1955, I delivered her again of a full-term infant with no difficulty. On May 16, 4 weeks after the delivery, I was called to her home because of pain in her abdomen. On May 9 and 10, 1955, she had had a temperature of 100. Examination of the abdomen revealed a tumor mass in the pelvis, nontender, which appared to be about 25 cm. in diameter. She was immediately referred for surgical consultation.

At operation on May 20, 1955, two large cystic tumors arising from the ovaries were found. Dark bluish nodules about one-half inch in diameter projected from the rest of the surface of each ovary. Each large tumor mass was about 8 to 9 inches across. The liver, on palpation, revealed many firm nodules of various sizes. She was sent home on May 31, 1955, with the diagnosis of metastatic ovarian melanoma with cystic formation. On June 21, 1955, her left breast was re-

moved because of "large expansively growing nodules of malignant melanoma." The patient died 3 months later with widespread metastases to the brain.

Case 2. The patient, gravida v, para i, was seen for her first prenatal visit on June 12, 1957. In 1942, she had had a full-term normal pregnancy. In 1946 she was operated upon for a 4 months' ectopic pregnancy. In 1948 and 1950 she had spontaneous abortions at 2 months.

The expected date of delivery was Nov. 3, 1957. On September 6, two weeks after the previous prenatal visit, she complained of vomiting 5 times that day and 12 times the day before. She stated that the day the vomiting started she became numb in all her limbs and face. She had had moderate headaches on all her previous visits and still had a headache. Previous blood pressure readings ranged from 100 to 106 systolic and from 54 to 64 diastolic. There had been no albumin in the urine. The VDRL was nonreactive. At the end of my questioning the patient and before I examined her, the husband asked me to look at some lumps in her right axilla which "she won't tell you about." There was a freely movable mass measuring about 7 cm. in the right axilla. It was not tender or red. The right breast was compatible with a pregnancy. The patient on close questioning revealed that the mass had appeared about the first part of August and had not grown in size since then.

She was immediately referred for surgical consultation and on Sept. 23, 1957, she was operated upon under local anesthesia. The surgeon's findings were as follows: Seemingly distinct from the breast tissue, which however was contiguous, was a group of three masses, one oval shaped and the other two spherical. The major mass had a greatest length of 4 cm., and the other two were about 1.5 cm. each in diameter. They were distinct from the surrounding tissues or the capsule which seemed to have a pedicle where the vascular supply entered.

The microscopic examination was reported as follows (four slides with four portions of tissue). The portions represented a neoplastic growth. Partially they were surrounded by a capsule of dense collagenous tissue. Within the capsule and also outside the capsule there were foci of lymphoid tissue of regular appearance and portions of fibrofatty tissue. However, invasion of the neoplastic tissue into the capsule was present. The neoplastic cells were present in cords and clusters. Focally there was the structure of alveoli.

The tumor tissue was supported by a netlike pattern of dense collagenous tissue. There was marked vascularity of the tumor tissue as well as foci of necrosis and presence of yellowish brown pigment. Within the tumor tissue there were also seen extensive foci of necrosis. The neoplastic cells themselves were polygonal in shape. There was a marked variation in nuclear size and in shape. The nuclei were round and oval shaped and occasionally also spindle shaped. Occasionally there were larger cells with two nuclei. In general the nuclei had prominent nucleoli. Mitotic figures were occasionally seen. As previously mentioned, there were areas of pigmentation. This reddish brown pigment was present in the cytoplasm; however, at times it is so much that the cellular structures cannot be recognized.

After the diagnosis of melanoma was made I questioned the patient about any previous skin lesions that had been treated. She stated that about 4 years previously a doctor had used a chemical on a skin lesion on the left anterior chest and on the right posterior parts of the chest. She received several applications. Contact with the doctor after this information revealed that he had no records about the treatment.

The patient was delivered of a full-term infant on Nov. 12, 1957. On April 21, 1958, the patient returned for surgical treatment because of recurrent growths in the original area of the right axilla. The surgeon removed four large nodes. On June 28, 1958, she had a plastic closure of the axillary wound. On Nov. 3, 1958, she was sent into the hospital for nitrogen mustard therapy and was treated for 5 days. Treatment with triethylenethiophosphoramide (thio-TEPA) was begun. Three series were given with no change. In fact the condition of the patient steadily declined, with metastases to other glands in the groin, neck, abdominal wall, and finally the other axilla. She died on March 20, 1959.

Summary

1. Two cases of pregnancy, one in which melanoma was discovered during gestation, and one in which melanoma was discovered about 4 weeks postpartum, are presented.

2. In one patient, age 29, a lesion from the skin of the back had been removed 4 years previously with a diagnosis of melanoma. In the other patient, some lesions on the anterior and posterior parts of chest had been treated with chemicals 4 years 61

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- 3. In Case 1, an abdominal tumor was found 4 weeks postpartum. In Case 2 axillary gland metastases were found in the sixth month of gestation.
- 4. In Case 1, laparotomy revealed metastatic lesions to the ovaries, peritoneum, and liver. Later the patient was subjected to a mastectomy because of large metastatic nodules of one breast. The second patient, in whom metastatic nodules were first found in the axilla, was subjected to operation for removal of the tumor masses, and the diagnosis of melanoma was first made. Later

more nodules were removed from the original site. Further treatment was attempted with nitrogen mustard and later with the new drug, triethylenethiophosphoramide.

5. Both patients died. It is significant that both patients had skin lesions removed. In one instance biopsy verified the diagnosis melanoma. In the other no definite diagnosis was attempted. However, each patient was subjected to a pregnancy and developed a florid disease. This strongly supports the probability that pregnancy may have produced, as Byrd and McGanity⁵ suggested, a recrudescence of the tumor and appreciably shortened the lifespan of the patient.

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Surgical procedures during pregnancy

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NONOBSTETRIC surgical complications demanding care during pregnancy initially and most frequently come to the attention of the obstetrician. His concern in the main is their effect on the outcome of the pregnancy and the well-being of the pregnant woman. However, as with medical complications, treatment of the nonobstetric surgical complication takes precedence over the pregnancy. Acute surgical complications and those suspected to be malignant demand prompt treatment. This is in the interest of the continued health of the pregnant woman and as a safeguard to the continued development and ultimate survival of the fetus.

In the past 18 years, we encountered 57 patients that had some form of nonobstetric operation during pregnancy (Table I). There were 50 patients requiring major surgical procedures and 7 in which minor procedures were done. Discussion will be limited to the 50 major surgical conditions encountered during pregnancy and their effect on the outcome of the fetus and the pregnant woman.

Ovarian cyst

The most common single lesion complicating pregnancy and treated surgically in this series was ovarian cyst. There were 22 such instances, or 44 per cent of all major surgical conditions listed in Table I. The frequency of ovarian cysts occurring during pregnancy has been variously reported by many¹⁻⁵ (Table II). Our incidence is 1:2,500 since during that period of time there were 54,750 deliveries. This agrees with the incidence reported by Falk and Bunkin⁴ but is much lower than that reported by Haas.⁵

The size of the ovarian cyst influenced the decision to operate. Cysts under 6 cm. were observed and not operated upon unless subsequently found to be enlarged or when acute emergency dictated operation (Table III). All ovarian cysts that were 6 cm. or larger were considered suitable for removal. The delay in removal was due to our awaiting optimum time for operation to safeguard the ultimate outcome of the pregnancy and to avoid early spontaneous abortion. The optimum time for removal appears to be during the second trimester of pregnancy.

Operations during the first trimester were performed on 11 patients while 11 patients were operated upon during the second trimester. There were no operations for this condition during the third trimester except when operation was done because of obstructed labor and these cases are not included in this report.

An additional reason for removal of ovarian cysts during pregnancy is the hazard these tumors are subjected to when permitted to remain untreated. The solid tumors, particularly, develop complications of torsion and have a high incidence of malignant transformation. Because of the difficulty in distinguishing clinically cystic from solid tumors, which according to Dougherty and Lund⁶ are more likely to be so changed,

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Table I. Conditions treated surgically during pregnancy

A. Major surgical conditions		50
Ovarian cysts	22	
Acute appendicitis	6	
Breast lesions	6	
Laparotomy (missed diagnosis)	4	
Uterine myomas	3	
Cholecystic disease	3	
Intestinal obstruction	2	
Strangulated hernias	2 2	
Laminectomy	1	
Thyroid disease	1	
B. Minor surgical conditions		7
Vulvovaginal lesions	4	
Pilonidal cyst abscess	1	
Integumental tumors	1	
Scalenus muscle biopsy	1	
Total cases	57	

Table II. Incidence of ovarian cysts operated during pregnancy

Authors	Incidence
Litzenberg ¹	1:1,500
Mathieu and Holman ²	1:102
Priest ³	1:1,085
Falk and Bunkin ⁴	1:2,500
Haas ⁵	1:316
Present study	1:2,500

Table III. Size of ovarian cysts at removal

Under 6 cm.	1	
6-8 cm.	 8	
8-10 cm.	3	
10-12 cm.	2	
12-15 cm.	8	

removal is urged even earlier —that is, when detected.

In the presence of an acute accident such as torsion, gangrene, rupture, infection, or intracystic hemorrhage, immediate operation should be done, according to Brock.⁷ Removal of other tumors which do not have the above characteristics may be delayed, especially if the size is below 6 cm., to await endocrine transfer from the ovary to the more fully developed placenta in the second trimester. This is advocated despite reports by Grimes and associates⁸ and Bonn,⁹ who found retention of the pregnancy despite accidental removal of corpus luteum with the extirpated cyst even in the first trimester.

There were 11 patients with dermoid cysts, 3 of which were bilateral. One patient was operated upon for bilateral ovarian cysts not knowing pregnancy coexisted until it was found at operation. The cysts measured 13 by 12 by 8 and 14 by 8 by 7 cm. Simple resection of both ovaries was accomplished. The uterus was felt to be the size of no more than a 6 weeks' gestation. The patient subsequently aborted about 2 weeks later despite antiabortive hormonal therapy. Two other patients with smaller bilateral dermoid cysts also had ovarian resection and continued their pregnancies to term. There were 4 corpus luteum cysts while 3 were simple cysts; 2 cysts were papillary serous cystadenomas, while the other 2 were a pseudomucinous cystadenoma and a paraovarian cyst, respectively.

Table IV. Summary of patients with abortion following operation for ovarian cyst

Weeks gestation	Time of abortion (post operative)	Type of operation	Type of cyst	Size	Hor- monal therapy
8	2 weeks	Bilateral ovarian resection	Dermoid (bilateral)	14×8×7 13×12×8	Yes
8	4 weeks	Oophorectomy	Dermoid (twisted) corpus luteum	$7 \times 7 \times 3$	No
8	2 weeks	Oophorectomy, appendectomy	Simple (twisted)	$15 \times 9 \times 6$	No
12	7 weeks	Oophorectomy	Corpus luteum	$8 \times 6 \times 8$	Yes
15	48 hours	Ovarian cystectomy	Corpus luteum	$15 \times 8 \times 7$	Yes

There were 17 term deliveries with 17 living babies. There were no premature births. There were, however, 5 spontaneous abortions.

The period of gestation at the time of the surgical procedure, the weeks of gestation when abortion occurred after operation, the type of operation performed, the type and size of removed lesion, and whether or not antiabortive therapy was given are listed in Table IV. Two patients aborted 2 weeks after operation, while one each aborted at 4 and 7 weeks after operation. One aborted 48 hours postoperatively. Three of the patients had oophorectomy; one had bilateral ovarian resection and one had ovarian cystectomy. Four of the patients had a corpus luteum in the cysts removed, while one did not show evidence of any corpus luteum in the cyst removed. Three of the ovarian cysts showed dermoid elements.

Two patients did not receive any antiabortive therapy while the other 3 received hormonal therapy. This therapy was given almost empirically to all other patients operated upon for ovarian cyst except the 2 mentioned above. Fifteen patients received progesterone therapy by intramuscular injection, one patient received estrogens only, 4 patients received both estrogens and progesterone. The value of the use of hormones in threatened abortion when no operation is performed is admittedly doubtful, and Haas⁵ in his report has also not been impressed of their effectiveness where surgical procedures were performed.

Acute appendicitis

In most comparable series reported10-14 appendicitis was one of the more common diseases found. It is one of the most serious surgical emergencies encountered during pregnancy. The incidence varies from 0.69 to 2.0 per cent. The symptoms vary depending upon the particular trimester the disease manifests itself and may thus be confusing because of their similarity to the usual symptoms of pregnancy-nausea, vomiting, and abdominal pain. However, Priddle and associates15 warn that nausea and vomiting after the fifth month is more significant than in the first trimester. The upward displacement from its pelvic location and the rotation¹⁶ of the usually protected downward pointing appendix to a transverse position at the iliac fossa at 16 weeks' gestation makes the diagnosis difficult. Later, near term, the appendix may become retrocecal15 or lie freely in the mid or upper peritoneal cavity in the region of the liver, still further delaying diagnosis and early surgical treatment. Delayed operation exposes the patient to serious complications, 17 such as perforation, peritonitis, uterine infection, thrombophlebitis, fetal mortality, and maternal morbidity and mortality.

All authors agree that leukocytosis per

Table V. Summary of histories in patients with acute appendicitis during pregnancy

Case	Weeks gesta- tion	Nausea and vomit- ing	Pain	Duration of symptoms	Temper- ature on admis- sion	WBC and % polys	Findings at operation
B. F.	24	Yes	RLQ	24 hours	99	20,000 (84)	Acute appendicitis
J. T.	34	Yes	General and RLQ	10 hours	100	21,000 (88)	Perforated appendix, peritonitis
H. G.*	32	Yes	RLQ	24 hours +	102	12,000 (79)	Perforated appendix, peritonitis
R. M.	24	No	RLQ	12 hours	100	15,000 (82)	Acute appendicitis
F. A.	22	Yes	RLQ	12 hours	99.2	20,000 (68)	Acute appendicitis, peritonitis
J. S.	24	Yes	RLQ	24 hours +	100.2	13,400	Perforated appendix, peritonitis

*Died 28 days postoperative and 23 days post partum.

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Table VI. Summary of data in 3 patients treated by myomectomy during pregnancy

Weeks gestation	Preoperative diagnosis	Operative findings	Post- operative complica- tions	Anti- abortive therapy	Result to	Type of delivery
12	Ovarian cyst	Pedunculated fibroid	None	No	Living, term	Vaginal
16	Solid ovarian cyst	Degenerating pe- dunculated fibroids (2)	None	Yes	Living, term	Vaginal
20	Fibroid urinary obstruction	Large fibroid	None	Yes	Living, term	Cesarean section

se is not an aid in diagnosis, since in normal pregnancy the leukocyte count may be 12,000. However, a rising leukocytosis determined at hourly intervals seems to be of greater value. This, together with fever, localized pain, rebound tenderness at different rightsided abdominal levels depending on the stage of pregnancy, and exclusion of usual pregnancy symptoms permits early diagnosis.

Six cases of acute appendicitis were encountered (Table V). The only maternal death was in this group. Four of the patients were in the second trimester of pregnancy and 2 were in the early third trimester. Five had nausea and vomiting, and 5 of these had pain referred to the right lower quadrant. Three of the patients had manifestations of the disease 10 to 12 hours, while 3 had symptoms of the disease for 24 hours before operation. There was no fetal mortality. Five patients were delivered of live babies at term; one patient went into premature labor on the fifth postoperative day and was delivered of a live baby which survived. The mother died 28 days postoperatively and 23 days post partum of multiple septic pulmonary emboli, pelvic thrombophlebitis, and bilateral parametrial abscess as found on autopsy.

Leiomyomas

As is well known, leiomyomas undergo many changes during pregnancy and may affect its outcome. During pregnancy, the leiomyomas enlarge, become edematous, and undergo degeneration, particularly red degeneration.

Palliation, watchful waiting, and other forms of expectant treatment should be the treatment of choice. When fever persists and pain does not abate and there is evidence of infection, gangrene, or suppuration, operation becomes imperative. 18-20 The abortion rate following myomectomy is high. According to Davids¹⁸ it is 34.3 per cent, and Childs and Douglass²¹ report it to be 54 per cent, while Roques²² lists it as 43 per cent, and this should be thoroughly considered prior to undertaking removal of myomas during pregnancy. Another deterrent to operative interference is the higher rate of hematoma and phlebitis with possible pulmonary embolization occurring following myomectomy in pregnancy than during momectomy in the nonpregnant state.

Despite the policy not to operate on myomas complicating pregnancy, 3 patients were surgically treated as listed in Table VI. In 2 patients the preoperative diagnosis of ovarian cyst was made, and both had pedunculated degenerated myomas. They had no postoperative complications and were delivered vaginally at term of living children. One patient had marked urinary obstruction as a result of a large myoma incarcerating the pregnant uterus in the pelvis and impinging on the neck of the bladder, preventing spontaneous micturition and relieved only by repeated catheterization. At operation a large myoma 10 by 12 by 6 cm. was enucleated from the posterior surface of the lower uterine segment. The patient received antiabortive therapy of estrogen and progesterone, in addition to sedation. She had an uneventful postoperative course. At term, she was delivered by cesarean section of a living child and had an uneventful course.

Intestinal obstruction

The incidence of intestinal obstruction during pregnancy is very low, but the condition must be suspected as present when vomiting and colicky abdominal pains persist with no defectation and no result from repeated enemas. An abdominal scar or history of pelvic inflammatory disease makes its presence highly likely. The persistence of these symptoms and x-ray evidence of fluid and air levels establishes a definite diagnosis.

It occurs more frequently in the third trimester of pregnancy, especially close to term, ²³ and is generally due to adhesions, external hernias, pedunculated tumors, volvulus, pregnancy ileus, or uterine pressure. ^{24, 25} Intestinal decompression, suction drainage, hydration, and attention to electrolyte balance must be included in the preoperative preparation. Cesarean section might be necessary initially to reach the site of the pathology, thus ignoring the outcome of the pregnancy²⁴ when the period of viability has not been reached.

Two patients were treated surgically for intestinal obstruction during pregnancy. Both were in the early third trimester (29 and 31 weeks) and both had a history of previous abdominal operation. After a period of observation, intestinal intubation, suction drainage, supportive intravenous therapy, and x-ray findings of fluid and air levels, they were operated upon. Adhesive bands were found in both patients kinking parts of the small intestine. These were divided. One patient had in addition a volvulus and an internal hernia. To reach the latter in the paraduodenal fossa, cesarean section had to be done with removal of a live baby which did not survive. The volvulus and hernia were reduced, establishing bowel continuity and restoring bowel circulation.

The other patient had a 2 cm. residual appendiceal stump from which an adhesive band originated. The appendiceal stump

was removed. This patient went into spontaneous premature labor 48 hours postoperative and was delivered of a premature (29 weeks) living infant which did not survive. Both mothers were discharged in good condition after an uneventful postoperative course.

Breast lesions

Of the 6 breast lesions listed in Table I, 3 were malignant and 3 were benign. All 3 malignant lesions were infiltrating duct carcinomas, and of the benign lesions 2 were fibroadenomas and one adenosis with hyperplasia of pregnancy.

Two simple mastectomies and one radical mastectomy were performed for the malignant lesions. All 3 of these patients had full-term deliveries and living children. Two of the mothers are still alive after 4 years.

It is felt that all breast lesions should be biopsied whenever they are found during pregnancy. Some authors²⁶ believe that pregnancy accelerates malignant growth and the duration of survival is shortened. This is in all probability due to the masking of the true lesion by engorgement and hypertrophy, and the increased vascularity influences greater growth, metastatic dissemination, and local invasiveness.

Last, while the actual mechanism is not known, the steroids effect tumor growth. Harrington²⁷ noted that of 11 women with major breast operations 7 went to full term and 4 had early abortion. He also stated that nothing can be found to recommend a postponement of operation for women in whom breast cancer coexists with pregnancy. Geschickter²⁸ agrees with this thought but adds that if the disease is too far advanced with distant metastasis palliation is indicated.

Laparotomy with error in diagnosis

The performance of a laparotomy as a result of a missed diagnosis occurred four times. Of this group the preoperative diagnosis of uterine pregnancy with ovarian cyst was made twice, tubal pregnancy once, and leiomyomas without pregnancy once. In all

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4 a normal intrauterine gestation was found. Two had no associated pathology with the intrauterine gestation, one had adhesions of small intestines without obstruction, and the one patient operated upon for leiomyomas had an intrauterine pregnancy with leiomyomas. Exploratory laparotomy only was done on one patient. Two had aspiration of the uterus for amniotic fluid to confirm suspicion of pregnancy and one had lysis of adhesions and incidental appendectomy. All these patients were delivered of living babies, 3 at term and one prematurely. There were no maternal complications following the operations.

Cholecystitis and cholelithiasis

As stated above, the frequent gastrointestinal symptoms of pregnancy can, in addition, mask the true symptoms of a diseased gall bladder. This is especially true in the first trimester of pregnancy. In this series 3 operations on the gall bladder were performed. Two patients had cholecystectomy with choledochostomy and one had simple cholecystectomy; two patients had incidental appendectomies. The postoperative course was normal in all the patients. One was delivered of a full-term infant, one patient is pregnant at present, and the other was not able to be followed. However, conservative therapy should be employed as often as possible.29

Other major surgical procedures

There were 4 other major surgical procedures performed. Two were for strangulated hernia, one subtotal thyroidectomy for tumefaction, and one a laminectomy for herniated disc. The operating time of the latter was slightly over 4 hours. No patient had any postoperative morbidity and all were delivered of healthy full-term infants.

Summary and conclusions

- 1. Fifty major surgical procedures performed during pregnancy have been reported and their effect on pregnancy wastage, perinatal mortality, and maternal mortality noted.
- 2. The largest group was 22 instances of ovarian cysts. Their management and effect on the outcome of pregnancy are discussed. Five early abortions occurred and the effect of antiabortive hormonal therapy is mentioned.
- 3. In acute appendicitis early diagnosis and early operation are the keys to good maternal and fetal survival. The only maternal death was in this group.
- 4. In intestinal obstruction similar early diagnosis and prompt operation yield good maternal recovery, but operation may force or precipitate premature termination of pregnancy. Two cases of perinatal mortality due to prematurity occurred in this group.
- 5. In all other categories where major operation was performed there was no early pregnancy interruption, no perinatal loss, and no maternal mortality.
- 6. The one maternal death following operation for acute appendicitis, the 2 instances of perinatal death following operation for intestinal obstruction, and 5 abortions following operation for ovarian cyst adds up to a greater fetal loss than is usually encountered.

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CURRENT OPINION

Re-evaluation

Diagnosis of euthyroid hypometabolism

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THE existence of a group of patients whose symptoms and basal metabolic rates (BMR) suggest hypothyroidism and, yet, who derive no benefit from desiccated thyroid has long been known. Such patients are usually regarded as having a "functional" lowering of metabolism secondary to over- or undernutrition, psychoneurosis, gonadal dysfunction, etc., or else, comprising the end fraction of a normal distribution curve of BMR's. A rather constant feature of such patients has been the presence of anxiety states, labile emotions, and easy fatigability. Since trials on desiccated thyroid or thyroxine were either ineffectual or poorly tolerated, such psychodynamic symptoms were believed to be the cause of the low BMR rather than the consequence of it. This view was widely accepted and the subject of "hypometabolism" without hypothyroidism put to rest until 1952, at which time a second, naturally occurring, thyroid hormone, L-triiodothyronine (T-3), with a potency exceeding that of thyroxine, was isolated from the blood by Gross and Pitt-Rivers and from the thyroid gland by Roche, Lizzitsky, and Michel. A report by Kurland, Hamolsky, and Freedberg in 1955 postulated the occurrence of a separate clinical syndrome of "nonmyxedematous hypometabolism" based on long-term observations of 4 patients whose abnormally low BMR's, previously shown to be resistant to thyroxine, rose to normal levels on a combination of thyroxine and T-3 or high doses of T-3 alone. The original study by Kurland and associates was subsequently followed by several reports and editorials2 confirming or refuting the existence of nonmyxedematous or euthyroid hypometabolism-the total of which settled neither the myth nor reality of the syndrome but tended to compromise on the rarity of its occurrence. Despite the skepticism voiced by the majority of endocrinologists over the claims made for T-3 in the treatment of so-called "hypometabolic" patients, the controversy was kept alive by the enthusiasm of practitioners who seemed to be getting favorable results with T-3 in several of their chronically tired, thyroid-resistant patients, and the gynecologists and urologists struggling with their infertility problems.

As a military physician dealing with a number of both tense, tired patients and in-

*Former Captain, United States Army Medical Corps, physician assigned SHAPE Headquarters, Paris, France. fertile couples, and in light of the impressive claims made for T-3 in early reports—particularly in the field of infertility—I started a careful search in our endocrine clinic in the winter of 1957 for bona fide cases of euthyroid hypometabolism.

Among approximately 500 patients screened by the methods to be outlined, 32 cases of euthyroid hypometabolism were diagnosed: an incidence of 6.4 per cent. Since, however, a sizable number of the psychoneurotic patients and those with suspected endocrine disorders were referred to the clinic for study by the area's physicians, this percentage cannot be said to represent the true incidence of euthyroid hypometabolism in the population at large.

The following five criteria were employed in the diagnosis of the euthyroid hypometabolic patient:

1. A symptom complex and clinical appearance suggesting hypothyroidism in certain respects and psychoneurosis in others. The 10 most common symptoms complained of by the typical "hypometabolic" patient were the following: fatigue, irritability and mood swings, lethargy, decreased libido, premenstrual tension, gastrointestinal symptoms, seborrhea of the scalp and/or hair loss, palpitations, myalgias and arthralgias, and shortness of breath. When the symptoms of the euthyroid hypometabolic patient were compared with those of the truly hypothyroid patient, several differences were apparent. The "hypometabolic" patient usually complained of morning fatigue in contrast to the late afternoon or early evening fatigue pattern of the hypothyroid patient; amenorrhea or oligomenorrhea was much more common in the "hypometabolic" woman than the metmenorrhagia accompanying hypothyroidism; oily, seborrheic skin and scalp were encountered instead of the dry, thick skin characteristic of thyroid deficiency; finally, the "hypometabolic" patient reported excessive rather than decreased sweating.

Body weight fell within normal limits in only 14 of the 32 "hypometabolic" patients; 14 patients were 20 per cent or more overweight and 4 patients, 20 per cent underweight. Two of the underweight patients were, in fact, suspected of having mild hyperthyroidism by clinical history until the report of their BMR's (both below -20 per cent) caused a hasty reversal of opinion.

The findings on physical examination were unremarkable except for the clinical or electrometric elicitation of the delayed or "hung-up" Achilles tendon reflex. Thyroid enlargement or nodularity was found in only 2 patients.

2. Presumably normal thyroid (thyroxine) function as shown by a normal proteinbound iodine (PBI) level and a normal rise in PBI following administration of 10 units of thyrotropic hormone (TSH). The experience of Jeffries' group3 with the response of both the PBI and radioactive I131 uptake to TSH in over 1,000 patients and my studies on 200 patients with use of the PBI response alone4 has clearly shown that the patient in whom the PBI level rises above 1.5 mcg. after administration of TSH is rarely hypothyroid at that time. In contrast, the patient whose PBI level fails to rise above 1.0 mcg. after administration of TSH usually has a thyroid deficiency and responds to thyroid hormone replacement both objectively and subjectively with permanent improvement. Among 70 patients found to have normal PBI levels and, yet, an abnormal Achilles reflex tracings and low BMR's, an adequate PBI-TSH response was seen in only 32 (the ones considered here to have euthyroid hypometabolism); the remaining 38 later were proved to have unequivocal hypothyroidism, the false-normal PBI levels being secondary to iodine contamination from various medications containing iodine or x-ray contrast media. Twenty-two of these 38 patients, originally started on T-3 in view of the possibility that they had euthyroid hypometabolism rather than hypothyroidism, later responded to equivalent dosages of desiccated thyroid in a completely similar fashion.* In contrast to this, no patient who

^{*}Equivalents used in this series: 37 mcg. T-3 equals 6 mg. desiccated thyroid.

had either euthyroid or "hypometabolic" tendencies and in whom the rise in the PBI level after administration of TSH was adequate showed significant long-term improvement on desiccated thyroid regardless of a suggestive history or initial response. It is worth emphasizing that the failure of the PBI level to rise adequately after the injection of a potent TSH preparation has reduced considerably the number of patients whose initial PBI levels were reported as normal or borderline low, and who might, therefore, have been included in the "hypometabolic" category.

3. Objective evidence of deficient endorgan metabolism as shown by a low BMR and electrometric recording of the Achilles tendon reflex. An accurate and economical means by which to record electrometrically the Achilles tendon reflex pattern in patients with suspected thyroid-metabolic dysfunction has recently been reported in the medical literature by Lawson.⁵ A modification and simplification of the apparatus originally reported by Lambert and his associates⁶ in 1951, the Lawson device, the kinemometer, has proved itself over 94 per cent accurate in the distinction between euthyroidism and hypothyroidism in over 3,000 patients tested.⁷ The fact that the standard BMR procedure requires complete relaxation on the part of the patient, coupled with the fact that the typical "hypometabolic" patient is a tense, anxious individual, often leads to a false elevation of the BMR, particularly if it is the first experience the patient has had with the BMR procedure. In contrast, the contraction phase (S-D interval) of the Achilles reflex tracing prolonged beyond 240 msec. has been a constant finding in this series of 32 "hypometabolic" patients and has proved to be the most reliable objective criterion one can use in screening such patients; the BMR was significantly low in only about half of the patients when measured for the first time (see Table I).

4. Negative response to placebos: equivocal or untoward response to desiccated thyroid given in dosages up to 300 mg. per day or tolerance. Upon completion of the initial work-up, all patients were given a 4 week trial on the placebo therapy. This procedure was followed in lieu of a double-blind study because of the fact that changes in the kinemometer tracing, repeated during each clinic visit, would reveal which patients were receiving active thyroid hormone medication. That the over-all response of the "hypo-

Table I. Pre- and posttreatment laboratory results in 32 euthyroid hypometabolic patients

				Average valu	ies and re	ange		
Therapy	No. of deter- mina- tions	None	No. of deter- mina- tions	Placebo	No. of deter- mina- tions	Thyroid	No. of deter- mina- tions	T-3
PBI (mcg.)	35	5.4 (4.2-7.7)		_		_		-
PBI rise after ad- ministration of TSH	32	2.7 (1.6-4.0)		-		-		
BMR	41	-15% (-33%- +7%)	32	-17.5% (-37%- +5%)	35	-13% (-33%- +11%)	104	-5% (-14%- +18%)
S-D interval, kine- mometer (msec.)	44	255 (240-290)	64	255 (230-290)	134	250 (230-300)	258	200 (170-240)
Serum cholesterol	32_	225 (180-350)	18	233 (160-370)	23	220 (165-360)	34	215 (140-345)

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metabolic" patient to placebos was poor was not surprising in view of the fact that these individuals had previously received numerous symptomatic drugs. At least two thirds of this group had taken or were currently taking one or more of the various tranquilizers. Weaning the patients off both tranquilizers and amphetamines proved to be difficult but essential, since it is strongly suspected that certain tranquilizers—reserpine in particular—can inhibit the end-organ action of exogenous T-3.

After treatment with placebos, patients were started on 120 mg. of desiccated thyroid and the dosage increased by increments of 60 mg. at biweekly intervals until either objective improvement or symptoms of intolerance resulted. It was a curious finding that less than half, or 15 of the 32 patients, could tolerate more than 120 mg. of the thyroid extract without toxicity, despite the fact that they later proved to be able to tolerate at least an equivalent amount of T-3 and, oftentimes much more. Among 10 patients showing an initial response to thyroid with improvement in symptoms and increase in BMR, such improvement was short-lived; both symptoms and BMR returned to pretreatment levels in 2 to 4 weeks despite continuation of the thyroid medication.

5. A favorable response, objectively and subjectively, to long-term treatment with proper amounts of T-3. The following three criteria were employed to judge unequivocal improvement on T-3: (a) alleviation of clinical signs and symptoms secondary to "hypometabolism," such as fatigue, nervousness, gonadal dysfunction, etc.; (b) a return to normal of the kinemometer tracing when the proper maintenance dose of T-3 was reached; (c) elevation of the BMR to normal limits and maintenance of a normal BMR over a minimal follow-up period of 5 months.

The above objectives were reached in these patients with average daily dosages of T-3 of 100 to 125 mcg. and a dosage range from 75 to 150 mcg. Patients were checked at biweekly intervals and the T-3 dosage adjusted according to the S-D interval of the kinemometer, the optimum being a contrac-

tion phase of approximately 200 msec. A noteworthy difference was observed in the response of the hypothyroid versus the "hypometabolic" patient to initial treatment with 75 mcg. of T-3 per day. The hypothyroid patient improved rapidly in the first 3 to 4 days, while the "hypometabolic" patient requiring 2 to 4 weeks and usually a higher dosage of T-3 before either symptomatic benefit or shortening of the S-D interval was noted.

What has proved to be a great practical advantage of the kinemometer over the conventional BMR or PBI in following patients given thyroid hormones is that an estimate of metabolic status can be obtained while the patient is still in the doctor's office and the thyroid dosage adjusted without delay. Although initiating therapy with small increments of T-3 in the range of 12 to 25 mcg. per day has been recommended by several authors, a worsening of the patient's hypometabolic state in the early days of treatment has been common enough and troublesome enough on this regimen that it is now our preferred practice to start patients in the younger age groups on 25 mcg. three times a day and raise this to 50 mcg. two times a day within 1 to 2 weeks. Although a precise explanation to account for the paradoxical worsening of the "hypometabolic" patient on low dosages of T-3 is not known, it is conceivable that 12 to 50 mcg. of T-3 may profoundly suppress the endogenous production of thyroxine via inhibition of the TSH release. Thus, treatment of a "hypometabolic" individual with 50 mcg. of T-3 (an amount which is insufficient to maintain a normal BMR in an athyreotic patient) may, by inhibiting endogenous thyroxine, make the patient more hypometabolic. For this reason, T-3 is logically given with the aim of completely replacing thyroxine as the circulating thyroid hormone, or else, in dosages insufficient to suppress TSH-as roughly reflected in the I131 uptake. As the latter amount is variable and difficult to approximate in any given case,8 the former procedure is recommended.

The controversy which has arisen over

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the alleged or actual existence of euthyroid hypometabolism is based on several reasonable objections. With the noteworthy exception of the original study by Kurland and his associates, the majority of case reports coneuthyroid hypometabolism have lacked the support of convincing laboratory data. Despite the fact that most present-day techniques which measure the functional capacity of the thyroid gland are within normal limits in the "hypometabolic" patient, such tests are, nevertheless, necessary to separate cases of euthyroid hypometabolism from those of actual hypothyroidism. "Double-blind" studies alternating T-3 with desiccated thyroid hormone and placebos suffer from the difficulty of using predetermined amounts of T-3 rather than dosages individually adjusted to meet metabolic requirements. That the dosages used in a "double-blind" study can be a crucial factor was shown in the study carried out by the British Research Council to determine the relative effectiveness of salicylates versus cortisone in the treatment of acute rheumatic fever.9 Likewise, the interpretation of a therapeutic trial based on subjective response alone is frought with error. Not only is a positive response to T-3 inconclusive evidence in favor of "hypometabolism" rather than the placebo effect, but a negative response does not rule out a true case of hypometabolism improperly or inadequately treated. If the therapeutic trial does not extend beyond the time-lag often seen in the "hypometabolic" patient before a response to T-3 is forthcoming, or if the patient is taking tranquilizers such as reserpine at the same time, results can be equivocal. Furthermore, in the absence of objective means by which to spot-check the patient's metabolic response (BMR, kinemometer, etc.) the nervousness produced by emotional stress or premenstrual tension can easily be confused with T-3 overdosage.

The theory originally proposed by several investigators to account for the occurrence of euthyroid hypometabolism, namely, that such patients are unable to deiodinate thyroxine to T-3 at the cellular level, has not met

with general acceptance or in vivo confirmation.10 In fact, the failure to find abnormalities in either the thyroidal iodine trap, the formation and release of thyroxine, binding mechanisms which transport thyroid hormones through the plasma, or the TSH response, raises the possibility that the causation of the "hypometabolism" may involve the neuroendocrine system outside the thyroid gland itself; that thyroid function is only secondarily affected (as in hypopituitary myxedema) resulting in an inhibition of T-3 formation and release, or else, exhaustion of thyroidal stores of T-3. In short, rather than being primary in the thyroid gland, "hypometabolism" may conceivably be a state of T-3 deficiency due to dysfunction at the corticohypothalamic level. Such a hypothesis, although attractive in accounting for the frequency of psychodynamic symptoms and obesity in the "hypometabolic" patient, remains but mere conjecture at the present time.

As in primary hypothyroidism, the "hypometabolic" patient shows evidence of disturbed gonadal function, such as amenorrhea or oligomenorrhea, anovulation, infertility, occasional uterine hypoplasia, impotency, frigidity, low or low-normal sperm counts with depressed sperm motility, etc. Among a group of 20 infertile couples, thoroughly studied from a genital and endocrinologic viewpoint, no less than 8 women and 3 men, a total of 9 couples, were found to be hypothyroid or "hypometabolic." Investigation of thyroid-metabolic function in a special group of 12 infertile men with sperm counts above 20 million and poor sperm motility revealed 5 individuals who had hypothyroidism, or were "hypometabolic" and who showed improved sperm motility on T-3 therapy. Of the remaining 7 men, all euthyroid-eumetabolic, only one showed significant benefit from T-3. Thus, in regard to treatment of the infertile couple with T-3, it is believed that such therapy is of certain value only in the patients where a diagnosis of hypothyroidism or "hypometabolism" is firmly established. Whether or not there is any rationale in giving T-3 to a euthyroid-eumetabolic patient in hopes that replacing thyroxine with T-3 as the principal circulating thyroid hormone will exert a "tonic" effect on a sluggish pituitarygonadal axis is not yet settled but seems doubtful in the light of present experience.

Finally, it is proposed that the favorable response brought about by T-3 therapy in this series of 32 "hypometabolic" patients was a specific and not placebo type response. In so far as possible, objective and not subjective criteria were used to judge improvement, the primary goals being a normal reflex pattern and BMR rather than alleviation of particular symptoms. Since Lawson

has convincingly shown that the kinemometer is affected only rarely by medical conditions outside of hypothyroidism and "hypometabolism," or few drugs other than the thyroid hormones,⁵ it is improbable that the changes noted in the S-D interval during T-3 therapy resulted from other factors than a changed metabolism. Considering that the majority of these patients had received numerous symptomatic medications in the past and were, in fact, inveterate pill takers and that these patients were informed that they might require lifetime maintenance on T-3, it is deemed unlikely that their overall improvement was artifactual.

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Relationship of leukemia in children to abdominal irradiation of mothers during pregnancy

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THE question of whether x-ray examination of the abdomen of a pregnant woman produces any harm to the fetus is one which is much discussed today. It is very difficult to obtain statistically significant data on this point because of the low incidence of the conditions being sought. This aspect of the problem has not been sufficiently examined in the pertinent literature and may well be at the root of our present difficulties.

In 1956 Stewart and co-workers,1 in a preliminary report, stated that x-ray examination of the abdomen had been performed during pregnancy more frequently in the group of mothers of children who subsequently developed leukemia or other malignant disease than in the group of mothers of the control children who had not developed malignant disease. The ratio was nearly 2 to 1.

In 1958 Stewart and associates² reported on the complete study, and the difference originally discovered between the two groups was borne out. There were 1,299 cases of malignant disease (619 leukemia, 680 other malignant disease) in children up to the age of 10 years, and a similar number of controls were used. It was found that x-ray examination of the abdomen during pregnancy had been performed in 178 mothers

in the malignant disease group. Among 1,299 controls, x-ray examination of the abdomen during pregnancy had been performed 93 times. (Among the 619 cases of leukemia, 69 of the mothers had abdominal x-rays during pregnancy, a slightly lower rate than the other malignancies, 1.6 times as often in the leukemia cases as in the controls.) Thus, abdominal x-rays during pregnancy had been performed 1.91 times as often in the malignant group as in the control group. It is of interest that x-ray examination of the abdomen had been performed in only 14 per cent of those cases in which a malignancy subsequently developed—in other words, 86 per cent of the cases of leukemia or other malignant disease developed without x-ray examination having been performed. Radiation is thus not a major cause of the development of malignant disease in children. In addition to x-ray examination of the abdomen, it was found that the incidence of virus infections and threatened abortion was significantly higher in the mothers of the children with malignant disease than among the control group. One other prenatal influence, excessive maternal age, appears to increase the risk of leukemia in children and to be related to the fact that this disease and Mongolism tend to occur together. The frequency of three postnatal eventsx-ray exposures in infancy, acute pulmonary infections, and severe injuries-was significantly higher for children who subsequently died of leukemia than for other children.

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There are several other figures in this report which deserve attention. It should be noted that congenital defects occurred in the group with malignant disease 75 times, in the control group 46 times. Mongolism appeared 17 times in the malignant disease group, and leukemia was present in 16 of these infants. None of the mothers of the children with Mongolism had had x-rays. There were no cases of Mongolism in the control group.

The family history was of considerable interest. For the group with malignant disease there were 2,119 liveborn siblings, of whom 8 died of malignant disease. In the control group there were 2,155 liveborn siblings, of whom 2 died from malignant disease. The health of the parents cannot be compared because of the method of selection of the controls. (Since the study method depended on questioning the mother, a control had to be rejected if the mother was not available.) There was information concerning 2,936 grandparents of the group with malignant disease, and of these 387 had leukemia or other malignant disease. There were 2,948 grandparents of the control group, of whom 316 had leukemia or other malignant disease. Information was obtained on 9,578 uncles and aunts of the group with malignant disease and of these 77 had some form of cancer. There were 9,425 uncles and aunts of the control group, of whom 55 had malignant disease. An increased familial tendency to malignant disease therefore certainly exists in the group of children who subsequently developed leukemia or other malignant disease.

J. C. S. Patterson made a study in the State of Louisiana covering the years 1951 to 1955, and discovered that the incidence of irradiation in utero was as follows: among 77 children who died of leukemia 27.3 per cent; among 70 children who died of other cancers 18.4 per cent.

Mills and associates³ reported on a 10 year observation of 155 children whose mothers had had x-ray pelvimetry usually during the last trimester of pregnancy. The dose to the fetus was estimated at 3.5 r. No cases

of leukemia or other malignant disease occurred in these children.

Rabinovitch⁴ went over some 4,000 x-ray examinations during pregnancy from 1940 to 1955, one third of these examinations being x-ray pelvimetries. There were only 6 cases of leukemia in children under 6 in the same period in this area and none of these children had been exposed to x-rays during the prenatal period.

Kaplan⁵ gave a preliminary report on a statistical study of this matter. He studied children with acute leukemia in California, and chose as controls their closest sibling and their most habitual playmate. There was a difference in the incidence of x-ray examination during the pregnancies resulting in the leukemic children and those resulting in the siblings, but not between the pregnancies resulting in the leukemic children and those resulting in the unrelated playmate.

Hempelmann and co-workers⁶ found in a sampling in a county in upstate New York that the incidence of pelvimetry in 1947 to 1957 was the same among the leukemic and the nonleukemic.

Material and method

We have been endeavoring at the Presbyterian Hospital to obtain information bearing on this point. We have started with a series of 260 cases of leukemia treated in Babies Hospital, Columbia-Presbyterian Medical Center. The place of birth of the child has been discovered and the mother's antepartum record was examined. In Stewart's study, the memory of the mother was depended on to some extent. In order to eliminate this possible inaccuracy, we have depended on hospital records entirely. After a case of leukemia was discovered, two controls were obtained. We used 2 children of the same parity born about the same time (usually within one week) in the same hospital. This eliminated variations in the use of x-rays in various areas and in primiparas as opposed to multiparas. The mothers' records were then studied and the occurrence of x-ray examination of the abdomen was noted.

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This proved to be an extremely time-consuming study. It is noteworthy that only 15 of these children were born at the Sloane Hospital, Columbia-Presbyterian Medical Center. Most of the rest were born in suburban and city hospitals, with a few in more distant areas. We were able to obtain complete information on a discouragingly low number, 62, from other hospitals, primarily because the older hospital records had been destroyed. This makes a total of 77 cases of leukemia with 156 controls (2 cases had 3 controls).

Results

Among the 15 babies born at Sloane Hospital, there were 2 whose mothers had x-ray pelvimetry; 6, chest films; and 5, dental x-ray examinations during pregnancy. Among the 30 controls, there were 3 x-ray pelvimetry (on 2 women), 2 dental x-ray examinations, and 7 chest films; 1 hip x-ray examination was done. (A few women had more than one type of x-ray.) In the cases where delivery was elsewhere, 2 mothers (in 62 cases of leukemia) had x-ray pelvimetry, and 4 had other types of x-ray studies, not abdominal. Five of the 126 control patients had x-ray pelvimetry, and 4 had abdominal x-rays; 2 had chest films.

Thus, in all, there were x-ray pelvimetry during pregnancy in 4 of the mothers of leukemic children and in 7 controls, with 4 other controls having abdominal films. In other words, there were prenatal abdominal films in 4 of 77 leukemia cases (5.2 per cent) and in 11 out of 156 controls (7.1 per cent). This difference is not statistically significant. Our figures, as far as they go, indicate no relation between x-rays of the abdomen in pregnancy and the subsequent development of leukemia in the child.

Comment

We have at hand several separate reports. One of these indicates that x-ray pelvimetry or other x-ray examination of the abdomen had been performed 1.9 times as often in a group of children who subsequently developed malignant disease as in a group of

children who did not. A second report states that x-ray examination was performed 1.7 times as often in the group which developed malignant disease. Our report, with 4 others, finds no difference in the incidence of x-ray examination of the abdomen between the mothers of children who developed leukemia and the mothers of those who did not.

Which of these is correct? Or are they all correct? The incidence of leukemia at present is about 4 cases per 100,000 per year.7 Competent statistical handling of this number would allow us to calculate the probability of obtaining any one of the three results noted above. It does not require extended knowledge of the theory of probability, however, for one to realize that with this small probability of 4 in 100,000 an extremely large number of cases would have to be obtained before statistical significance was achieved. All of us are familiar with the vagaries of the laws of chance. The usual relation of boy babies to girl babies is 106 to 100, so that there is approximately a fifty-fifty chance that any baby born will be of either sex desired. On one occasion at the Sloane Hospital for Women there occurred the consecutive births of 28 boys. Those who visit Las Vegas or Monte Carlo do so with the knowledge that while statistics work out in the end, one can always hope for a favorable variation in their present operation. It seems to us, therefore, that a causal relation between x-ray examination of the pregnant woman and the development of malignant disease in her offspring has not been demonstrated. On the other hand, one may say just as certainly that a lack of relation has also not been demonstrated. Our figures do not allow us to answer this question at present.

Let us now look at another side of the picture. Leukemia can certainly be induced by radiation.⁸ This has been amply established in animal experimentation. It has been established in the survivors of the atom bombings in Japan,⁹ and in a group of adults treated with radiation for ankylosing spondylitis,¹⁰ as well as in a group of children receiving x-ray treatment to the

thymus.¹¹ Leukemia is more common among radiologists in the United States than among other physicians. It must be noted, however, that no increased incidence of leukemia has been demonstrated following a smaller dose than 100 rads. Whether or not the incidence of leukemia is related in a linear manner to an increase in the dose radiation has been recently discussed by Brues.¹² He comes to the conclusion that a linear relation between dose and effect cannot be proved and suggests that a "disordered state of tissue" must be produced by the radiation in order for leukemia to occur. This implies a relatively large dose.

Lewis,13 on the other hand, has produced an ingenious calculation based on the linear theory through which he arrives at the statement that one unit of radiation increases the risk of development of leukemia by two chances in one million per year. Remembering that the data on which these figures are based may be faulty to begin with, we may derive a statement of the theoretical risk from x-ray pelvimetry. When four films are obtained the dose to the fetus is about 2 r.* This would increase the risk of leukemia by 4 per million per year. Since the risk at present is 4 per 100,000 per year, the total risk incurred would be 4.4 chances per 100,000 per year.

X-ray examination of the pregnant woman is indicated for two main reasons. She may have a disease which is not directly related to the pregnancy but which constitutes a threat to her life and to the life of the unborn child. X-ray examination in this instance may not only save her life but save the life of the child. More often x-ray examination is required because of the presence

of disproportion or malposition of some kind. When such an abnormal condition exists, the fetus and the mother are both in considerably increased danger compared to that of the normal patient. The risk of death to the fetus with delivery from below in the presence of a high degree of disproportion is at least 5 per cent and may be as high as 20 per cent. The mother is also in danger when such a traumatic delivery is carried out. Cesarean section, on the other hand, also carries a certain risk to mother and baby, probably in the range of 5 per thousand. Discovery of the type of disproportion allows us to deliver the baby in a manner which is safest for the baby and the mother. X-ray examination is a powerful aid in this situation. X-ray examination should therefore be performed in those cases in which clinical examination determines the need for it. Routine x-ray examinations should not be performed. We thus return to the final remark of Stewart, Webb, and Hewitt that these findings "underline the need to use minimum doses for essential medical x-ray examinations and treatments."

Summary

- 1. The frequency of x-ray examination of the abdomen during pregnancy in the mothers of a group of children who died of leukemia is compared with the frequency of such examination in the mothers of a control group of children.
- 2. Among 77 mothers of children who died of leukemia, prenatal abdominal x-ray examination was carried out in 4, an incidence of 5.2 per cent. Among the 156 controls, abdominal x-ray examination was carried out in 11, an incidence of 7.1 per cent.
- 3. These figures neither prove nor disprove a relation between x-ray examination of the abdomen during pregnancy and the subsequent development of leukemia in the child.
- 4. It is concluded that x-ray examination should continue to be performed during pregnancy in those cases in which clinical examination determines the need for it.

^{*}Since we considered that the liver, spleen, and spine would be more important in leukemia, we asked our physicist, Mr. F. B. deFriess, for figures. From charts and films he estimated that in an occipitoanterior presentation the fetal spine would receive 300 mr. in the anteroposterior and lateral views and 1 r in the pair of stereoscopic views. Therefore 2 r seems a generous estimate of the amount the blood-forming organs of the fetus might receive in the maximum examination done at Sloane Hospital, i.e., anteroposterior and lateral standing views of the pelvis at 40 inch distance (Ball method) and anteroposterior stereoscopic views at 25 inches (Caldwell-Moloy method).

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Reviews | Abstracts

Edited by LOUIS M. HELLMAN, M.D.

Reviews of new books

The Operations for Inguinal Hernia. By Mark M. Ravitch and James M. Hitzrot, II. 64 pages, 36 illustrations including 4 in color. St. Louis, 1960, The C. V. Mosby Company.

This small book has nothing to do with obstetrics and gynecology but it came into the editor's hands through such a combination of circumstances that some note seems merited.

A year or so ago I sent the author a book on hernia suggesting that he might wish to review it although I considered the subject of little current interest, especially in view of the dramatic progress of surgery. Needless to say no review was forthcoming. Within the past week having required some repair by the senior author, following an accident cutting cord wood, he presented me with Contributions of Bassini, Halsted, Andrews, Ferguson, Lotheissen to The Operations for Inguinal Hernia, remarking that now that he had me captive I might as well review a good book on hernia.

Remembering the toils of countless medical students and surgical interns trying to learn who planted the cord where and which way the fascia was imbricated I found this book a gem of medical history. Here are presented a picture and brief biographical sketch of the major contributors to the hernia operation. Bassini's original pictures are reproduced in color, and those of Halsted, Ferguson, and Andrews in black and white. The Bassini-Halsted priority argument is completely documented with credit going as Halsted freely acknowledged to the former. Finally, there is clearly presented the genesis and technique of Halsted's final operation which the late Dean Lewis always called the Hopkins Hernia.

But for a few stitches in the head and a formerly biased view about those who write of hernia operations I might have missed a fascinating bit of surgical history—well collated and clearly presented.

Obstetrical and Gynecological Pathology. By R. E. Rewell. 435 pages, 19 tables. London, 1960, E. & S. Livingstone, Ltd., \$10.00. Though intended for postgraduate students, most of the entities in this book are not discussed in great detail but only in broad aspects. Consequently, it would be of more value to the medical

great detail but only in broad aspects. Consequently, it would be of more value to the medical student than to those who have much knowledge of the subject. Even for the medical student there is much that could be desired. There is no adequate classification of ovarian tumors or the relative frequency of bilaterality and malignant development.

One of the most important aspects of a textbook on pathology is the photomicrographs. These are used as references by other observers. The illustrations in this text are, by and large, very poor, and there are too few. This is very evident in the chapter on cytology.

In general this book does not provide anything outstanding and it is questionable how much demand there will be for it.

Contributions of Obstetrics and Gynaecology. By V. N. Shirodkar. 159 pages, 196 figures. Baltimore, 1960, Williams & Wilkins Company. \$8.50.

The author is a well-known specialist from Bombay who has seen a great deal of clinical material and has performed several thousand gynecological and obstetrical operations. His book describes some of the operative techniques which he has devised and one of these is the operation for uterine prolapse. The author advises the extended Manchester procedure which

is demonstrated by serial illustrations. In selected cases, if his initial operation fails (5 per cent) the sling procedure is employed.

In certain women who have habitual abortion in the second trimester the author suggests his well-known strap operation. An excellent group of illustrations reveal the technique. He advocates cesarean section for the delivery after a successful repair.

In another section of the book Shirodkar reports on surgical correction of the blocked Fallopian tube and cites 140 tubal implantations with a 35 per cent pregnancy rate and a 90 per cent postoperative tubal patency rate. Detailed analysis of the cases are not given but he does describe his operation and suggests reasons for his high rate of success. He attempts to grade tubal occlusions in a manner similar to the classification used in carcinoma of the cervix. The idea is a good one and merits further exploration.

The final procedure which is described in detail is the creation of an artificial vagina from a piece of sigmoid colon. Thirty-seven of his 40 patients did extremely well. The last part of the book is a summary of various papers previously contributed to the scientific literature by the author.

The book is a valuable asset to those who are interested primarily in the four operations described, but it is of limited use.

Thank You, Dr. Lamaze. By M. Karmel. 190 pages. Philadelphia, 1959, J. B. Lippincott Company.

In Thank You, Dr. Lamaze, Marjorie Karmel describes her experiences with Dr. Lamaze's adaptation of the Pavlovian method of natural childbirth based upon the conditioned-reflex theories of the famous Russian physiologist.

Mrs. Karmel's ability to write interestingly and amusingly provides easy reading for the expectant mothers who want to know more about the psycho-prophylactic method of childbirth. But more than this, the keenness of the author's insight and observations gives emphasis to the analogy of varying methods of natural childbirth. She attempts to allay the confusion which may exist for expectant parents by adequately explaining that all the different systems of natural childbirth attempt to eliminate fear by educating women to the process of childbirth and by reorganizing the institutional setup.

The book is divided into two parts—experience

in Paris and experience in New York. The two experiences present quite a contrast. The accidental findings in Paris and the curiosity in what was ahead in her venture into motherhood envelop her revelation with a mysterious air. In New York she was already convinced of what she wanted and was searching to bring back a little of the past. This gives the reader a feeling of a more positive approach to a method of childbirth and a doctor who could carry out her wishes. The manual of information and practical exercises for painless childbirth by Mesdames Rennert and Cohen, and the suggested reading, are useful additions.

Childbirth Without Pain. By Pierre Vellay and others. 216 pages, illustrated. New York, 1960, E. P. Dutton & Co., Inc. \$3.95.

There are several books today on the market dealing with the abolition of pain during child-birth without the use of analgesic drugs. Dr. Pierre Vellay has written down in his readable book the method of the late Dr. Fernand Lamaze which he stated is based on the Pavlovian concept of conditioned reflexes. As is stated on the cover Dr. Lamaze wished to teach his mothers-to-be "control and understanding of the process of childbirth which made her the cooperator instead of the victim of her own body."

The book is divided into three parts. Part one, Background to the Method, reveals the history, the theory, and how the method differs from Dr. Read's. "The Lamaze method depends on words as therapeutic agents—psychoprophylaxis, verbal analgesia based on the training of pregnant women." The second part takes up the eight lectures that are given to the fathers- and mothers-to-be. The third section, which is approximately one half of this book, deals with the personal accounts of the method from foreign women giving birth in France. Primiparous and multiparous women, women who have already experienced childbirth without pain, women difficult to condition, and the failures are presented.

The reviewer would like to comment about the mixed feelings in existence as to whether or not analgesia and anesthesia should be used in labor and for delivery. Excellent work has been published which shows that fetal outcome is better when carefully planned and administered analgesia and anesthesia are used. However, the services of a skilled obstetrical anesthesiologist are not always available and nearly every obstetrician can recall one or more unpleasant

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adich events when anesthetic agents were used for childbirth. A simple, easy-to-use method is certainly needed, and everyone is aware of the fact that an enlightened, prepared mother-to-be makes the obstetrical and anesthetic management of the labor and the delivery a pleasant and easier task. This book which will help prepare the mother-to-be is a step in the right direction and is recommended by the reviewer.

Complications in Surgery and Their Management. By C. P. Artz and J. D. Hardy. 1075 pages, 272 figures. Philadelphia, 1960, W. B. Saunders Company. \$23.00.

Drs. Artz and Hardy have made this a carefully thought-out and planned, well-written, and handsomely published volume. The preface is preceded by a quotation suggesting that the record of disasters is a more valuable source of information than the chronicle of safe achievements. This is in contrast to the statement, perhaps apocryphal, of Roald Amundsen when a titillated feminine dinner partner asked him to describe his most perilous adventure, "Madam," he said, "good explorers do not have adventures."

Unfortunately, good surgeons and their patients not infrequently do have perilous adventures, and the nature and types of these, and their treatment, are beautifully discussed in most of these chapters. In preparing such a book as this, one would have had the choice of describing complications according to the system involved, and irrespective of the type of operation performed, or, as in the present volume, for the most part, operation by operation. The 69 contributors are almost all well-recognized authorities in the subjects which they have written, and their writing reflects their competence. The laudatory biographical vignettes which precede the individual chapters may be pleasing to some contributors and must be embarrassing to others. The value and propriety of such biographical sketches in current works may perhaps be questioned, but this reviewer has a strong feeling that, to the medical historian or surgical student a few generations from now, these descriptions and evaluations will lend interest to the volume.

Inevitably most of the contributing authors have concentrated on the prevention of complications, and the result is essentially a textbook of surgery. The only serious criticism which can be leveled at the book is due to the presence of a certain remoteness of discussion of many of the complications, which, no doubt, is inevitable

when chapters on difficulties in surgery are written by the people who have the fewest.

Lurid books on mistakes and complications in surgery have been written, but this is not one of them. To describe the effects of hemorrhage in the neck after a thyroidectomy the author had to cite an instance of hemorrhage after reconstructive operation upon the carotid artery.

The coverage is broad, and it includes the surgical specialties, among them pediatric surgery. There is a remarkably detailed and useful table of contents which serves as an excellent index in addition to the very thorough standard index.

As a specialized textbook of surgery this book is valuable in its own right. From the standpoint of a book designed to aid the surgeon faced with a complication in surgery, it might perhaps have been written in a more detailed and specific way, with particular reference to the minute recognition of individual complications. The omission of the relatively standard descriptions of the basic principles of surgery in the various organs, and pathological conditions, might have allowed for more detailed exposition of the nature of complications. The recognition of the existence of a complication is frequently the single greatest obstacle to the patient's recovery.

Anatomy—A Regional Study of Human Structure. By E. Gardner, D. J. Gray, and R. O'Rahilly. 999 pages, 40 tables, 82 figures, 65 plates. Philadelphia, 1960, W. B. Saunders Company. \$15.00.

This book will present a powerful challenge to the inherited status of the old-fashioned compendium of anatomy. The volume of material can be reasonably digested by the undergraduate medical student in the time allotted in the modern shortened courses in anatomy. The style of presentation is simple and direct, almost terse. The sentences fairly overflow with facts. The illustrations are for the most part helpful, especially where a simple line drawing is used to explain a particular concept. References to the literature are adequate and up to date and should readily guide the more advanced student to recent sources of information.

The first 104 pages of this book are devoted to general anatomy which is somewhat systemic in character; however, the general principles stressed are applicable to all regions of the body. Since the object of a textbook should be to encourage the students' inquiring instincts, per-

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haps more emphasis could have been placed on the presentation of ideas and problems in anatomy even at the expense of omitting some of the facts. There is an excellent correlation of structure and function throughout the book which makes the book unique in this respect. It may be unfortunate, however, that living and radiological anatomy are presented as separate sections for each region, and thus may appear to the student as simply additional material to be learned. The difficult task of utilizing living and radiological anatomy as a tool for a more complete understanding of human anatomy has therefore not been fully achieved. The treatment of muscle function is excellent and a welcome relief from the long lists of muscle actions of the older textbooks. In most textbooks of anatomy there appears to be confusion regarding the terms "muscle action" and "muscle function" with the result that the terms are often used interchangeably. The authors clearly define muscle action and function in the general anatomy section. However, in describing particular muscles, the authors use the term "muscle action" which, to this reviewer, appears to contradict their definition of the term.

Bilharziasis of the Ovary in Egypt. Egyptian Society of Gynecology and Obstetrics Monograph Series No. 1. By M. Alaedine Shafeek. 48 pages, 45 illustrations. Cairo, 1958. C. T. Soumas & Co. Bilharziasis of the ovary is not rare in Egypt. It constituted 8.2 per cent of all ovarian lesions examined in the Pathological Department of the Ministry of Public Health from 1946 to 1955.

Bilharzial oophoritis is more common in Lower Egypt and is caused mostly by *Schistosoma haematobium*. Commonly the condition is bilateral and there is an associated bilharzial salpingitis, and, not uncommonly, follicular and corpus luteum cysts.

Pathologically one sees fibrosis of the ovary, chronic perioophoritis, thickening of the tunica albuginea, variable amounts of ova, and bilharzial pseudotubercles.

The author feels the association of ovarian neoplasms with bilharziasis is mere coincidence.

It is a disease of adults and may be asymptomatic. The condition should be suspected when there is a history of exposure or evidence of bilharzial infection in other parts of the genital tract or other organs.

The proper treatment in most cases is medical

(fovadin or tartar emetic) followed if necessary by conservative operation.

Cancer of the Cervix—Diagnosis of Early Forms (Ciba Foundation Study Group No. 5). Edited by G. E. W. Wolstenholme and M. O'Connor. 114 pages, 27 figures. Boston, 1959, Little, Brown & Company. \$2.50.

This informative pocket-sized book is a concise report on the works and related discussions presented at the Study Group on "Cancer of the Cervix—Diagnosis of Early Forms" on Friday, May 8, 1959.

The papers covered topics such as the classification, histopathology, cytopathology, and early diagnosis of cervical carcinoma. Along with these cogent presentations, there were significant studies of the biology and morphology of the cervix and their relationship to carcinoma of the cervix. Following each presentation there were verbatum discussions by prominent investigators in this field. The discussions were for the most part factual, enlightening, and interesting but at times seemed a trifle irrelevant.

G. H. Friedell, A. T. Hertig, and P. A. Younge. 154 pages, 97 figures, 19 tables. Springfield, Ill., 1960, Charles C. Thomas, Publisher. \$7.50.

This timely monograph, starting with the historical background, presents a coherent review of the subject of carcinoma in situ of the uterine cervix. It recapitulates much of this historical background in describing the accumulation, by addition and attrition, of the 235 cases over a period of 36 years (from the Free Hospital for Women in Brookline, Massachusetts) that form the basis for this review.

The thoroughness with which the specimens obtained are prepared and studied in the pathology department is very impressive and serves to emphasize the need for thorough collaboration between clinician and pathologist. Every pathologist, as well as every clinician who is faced with the problem of rendering a decision on the presence or absence of carcinoma in a cervical biopsy, can benefit from study of the chapter on pathologic anatomy. It is emphasized that the more thorough the study, the smaller will be the group of questionably invasive neoplasms. The same discernment does not carry over to the chapter on clinical find-

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ings. It is not stated clearly enough that symptoms due to carcinoma in situ do not exist and that symptoms that are present are due to other factors incidentally coexistent. Similarly, in remarking on the general appearance of the cervix in these cases, it is stated that only 14.5 per cent of the patients had "normal" appearing cervices. This figure, in the absence of a control figure of incidence in a similar group without carcinoma in situ, with use of the same criteria, is of little bearing, and can be misinterpreted.

The importance of the nonspecific Schiller test in picking out areas with carcinoma in situ is well demonstrated. Furthermore, the significance of cervical smears in selecting patients for biopsy is emphasized. The authors state that when smear and biopsy (in areas indicated by a positive Schiller test) are used as complementary diagnostic methods, failure to estab-

lish the diagnosis in carcinoma in situ of the cervix should not exceed 2 per cent. It is to be noted that the authors prefer multiple punch biopsies taken with a large, square-jawed punch and endocervical curettage as their method of establishing the diagnosis and excluding invasion.

As to therapy, they apparently prefer total hysterectomy in most cases, and more conservative therapy (conization, amputation) in a small, well-selected (on the basis of age and desire for children) group of cases. There is due emphasis on the need in all cases for posttreatment follow-up at regular intervals.

If all physicians responsible for the care of women familiarized themselves with the contents of this monograph, a great stride would be made toward the realization of the concept of "cancer of the cervix: a preventable disease."

Selected abstracts

The Lancet

Vol. 2, Oct. 10, 1959.

*Tovey, Geoffrey H., and Valaes, T.: Prevention of Stillbirth in Rh Hemolytic Disease, p. 521.

Tovey and Valaes: Prevention of Stillbirth in Rh Hemolytic Disease, p. 521.

Following the suggestion of Kelsall and Vos (M. J. Australia 1: 349, 1952) that the severity of disease in the baby is closely related to the level of anti-Rh in the mother's serum determined by the indirect antiglobin technique, a series of 200 babies born to mothers who had not previously carried an affected child (1) and 62 babies whose mothers had already had Rh antibodies during a previous pregnancy (2) was studied. The antibody levels discussed are the maximum titers obtained between the thirty-fourth and thirty-sixth weeks of the pregnancy.

In (1) there were no stillbirths and only 45 per cent of the babies needed transfusions if the mothers' antenatal antiglobin titer was less than 1:10 (59 patients). Among the 84 babies whose mothers' antenatal antibody titers were 1:10 but less than 1:40 there was one stillbirth

and 71 per cent of the babies required transfusions. However, among the 57 babies whose mothers had an antenatal antiglobin titer of 1:40 or higher there were 24.5 per cent still-births and 98 per cent of the babies required transfusions.

In (2), although there were no stillbirths and no transfusions were needed in the babies whose mothers had antenatal antibody titers of less than 1:10, when the latter was 1:10 but less than 1:40 the stillbirth rate was five times higher (6.25 per cent) than when the mother is carrying a first affected baby, and 80 per cent of these babies required transfusion. In (1) and (2) the results are much the same when the antiglobulin titer is 1:40 or higher. However, the percentage of stillbirths in (2) would certainly have been higher but for the fact that most mothers who had previously had a severely affected or stillborn baby were delivered prematurely. That there were more severely affected babies in (2) than in (1) when the mother's antibody titer was 1:10 but less than 1:40 tends to confirm the opinion of Kelsall, Vos, and Kirk (Brit. M. J. 2: 468, 1958) that duration of exposure of the baby to these anti-

^{*}These articles have been abstracted.

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bodies is important in determining the severity of disease in the baby.

The cord blood was studied, and a close correlation between the hemoglobin level, serum bilirubin level, and maternal anti-Rh titer was found.

In (1) when the maternal Rh titer is 1:40 or higher the risk of death found before 34 weeks of pregnancy was 3 per cent; it was 5 per cent at 34 weeks, 3 per cent between 35 and 36 weeks, but 20 per cent after 37 weeks of pregnancy. These figures suggested that two thirds of the stillbirths might be prevented if the baby were delivered 21 days before term. Few additional deaths would be prevented unless the pregnancy were terminated at or before the thirty-fourth week, and this would introduce too many hazards for prematurity. Therefore, the practice has been adopted to recommend premature delivery 21 days before the expected date of delivery if the mother's anti-Rh titer has reached or exceeded 1:40 by the thirty-sixth week of pregnancy.

When the mothers have previously had an affected baby (group 2) the smallness of the series did not provide such clear indication and the antenatal antibody titer could be used as only one criterion. At present the authors believe that if the previously affected child did not require treatment and if the maternal antibody titer is less than 1:10 the pregnancy may be allowed to proceed to term. However, if the preceding baby required treatment or if the maternal antibody titer has risen from that observed in the preceding pregnancy (1:10 or 1:20), pregnancy should be terminated 21 days before full term because the stillbirth risk in this group approaches 10 per cent.

If the maternal titer is 1:40 or greater and the father is homozygous the risk of a dead baby is about 1 in 3 and the death generally occurs before the thirty-seventh week. Therefore, premature delivery is advised 35 days before full term. If the father is heterozygous-positive and if no change in maternal titer occurs, the delivery is delayed until 21 days before term. In all of these recommendations the size of the baby and the accuracy of the time of gestation are, of course, considered in determining the optimum time for delivery.

The technique employed in the antibody titrations is described in an appendix. Close standardization of end points between various laboratories is difficult so that the critical titer of 1:40 used in this study may be somewhat different from that found in different laboratories. Inasmuch as the only hope of preventing some of the stillbirths from hemolytic disease of the newborn is premature delivery (when weighed against the risks of the latter) each laboratory should evaluate the results of the test as it is done in that laboratory until such a time as standardization of end points can be obtained.

David M. Kydd

Oct. 15, 1960.

*Hayward, M. D., and Bower, B. D.: Chromosomal Trisomy Associated With the Sturge-Weber Syndrome, p. 844.

*Tough, I., Buckton, K., Baikie, A. G., and Court-Brown, W. M.: X-ray-Induced Chromosome Damage in Man, p. 849.

Hayward and Bower: Chromosomal Trisomy Associated With the Sturge-Weber Syndrome, p. 844.

Culture of the bone-marrow cells from a boy almost 4 years of age with Sturge-Weber syndrome (mental retardation, convulsions, portwine nevus, buphthalmos) disclosed that there were 47 chromosomes. After matching, it was concluded that the extra chromosome represented a trisomy of No. 22. Only further study will prove that this represents a specific defect, particularly in view of the discovery of a normal male with a trisomy chromosome No. 19 by Fraccaro, Kaijser, and Lindsten (Lancet 1: 724, 1960).

David M. Kydd

Tough et al.: X-ray-Induced Chromosome Damage in Man, p. 849.

In this preliminary communication 2 patients who received x-ray treatment for ankylosing spondylitis were studied. The first patient received a total skin dose of 1,500 r in 10 equal daily fractions over the entire spine and sacroiliac joints. Study of chromosome preparations made from blood cultures before and after this treatment showed evidence of considerable chromosome damage (significant changes in count distribution and increases in the number of cells carrying structural abnormalities).

The second patient received one dose of 250 r to the skin overlying the spine only. Cell preparations were made before and serially for 10 days after the treatment. Within 24 hours the percentage of cells with 46 chromosomes had fallen from 93 to 72, due to a remarkable in-

crease in cells with 47 chromosomes (from 1 to 21 per cent). In addition the percentage of cells with structurally abnormal chromosomes rose from 1 to 22. Three days later the unusually low count of modal cells was still present and on this day the percentage of cells with chromosome structural abnormalities reached a maximum.

By the fifth day the percentage of modal cells had returned to the pretreatment limit and so remained. Although the percentage of cells with structural abnormalities of the chromosomes had declined by the fifth day, 9 to 10 percent of the cells were still abnormal on the ninth and tenth days.

In both patients unusual numbers of polypoid cells were seen after therapy.

Although much more work will be necessary to understand the pattern of the changes, particularly the effect of varying the total dose and dose rate, x-rays readily produce chromosome damage which can be detected in cultures of human blood cells.

David M. Kydd

Oct. 22, 1960.

*Fraccaro, M., Kaijser, K., and Lindsten, J.: A Child With 49 Chromosomes, p. 899. Fraccaro, Kaijser, and Lindsten: Child With 49 Chromosomes, p. 899.

A boy aged 7 born of normal parents and with one normal brother 1 year old was noted to have a peculiar facies (flat occiput, epicanthic eyefolds, etc.) a divided scrotum, congenital heart disease (ductus arteriosus), and apparent mental retardation. Minor abnormalities of the right kidney were found by urography. A gonadal biopsy disclosed a testis devoid of normal structure with an epididymis.

Cells were cultured from bone marrow and skin of the patient and his mother, from the bone marrow of his father and from the skin of his brother. The interphase nuclei were sexchromatin positive in the patient and in his mother and negative in the others. In both primary and transferred cultures 49 chromosomes were counted in the cells from the patient and 46 in the cells from the other members of the family. Study of the chromosomes led to the conclusion that there was trisomy for chromosomes No. 8 and No. 11 and that the sex chromosomes were of the XXY type rather than a trisomy of No. 21. The patient could not be diagnosed as having either Mongolism or Kline-

felter's syndrome even though he had certain symptoms of both. Although the origins may be obscure, multiple chromosomal abnormalities are not very rare.

David M. Kydd

Oct. 29, 1960.

*Badawy, A. H.: Non-union of Uterine Wounds, p. 944.

Badawy: Non-union of Uterine Wounds, p. 944. The histories of 3 patients are reviewed to emphasize the belief that most dehiscences of cesarean scars in subsequent pregnancies are the result of non-union after the original operation. Hemorrhage may result if the placenta bridges the gap. However, the condition may be asymptomatic until the time of delivery, particularly when the scar is in the lower uterine segment where the peritoneum is much less likely to be ruptured until it becomes greatly stretched during labor.

David M. Kydd

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Nov. 5, 1960.

*Gatenby, P. B. B.: Anticonvulsants as a Factor in Megaloblastic Anemia in Pregnancy, p. 1004.

McFayden, I. R.: Postpartum Pre-eclampsia, p.

Gatenby: Anticonvulsants as a Factor in Megaloblastic Anemia, p. 1004.

In a previous report of 100 instances of megaloblastic anemia in pregnancy (Gatenby and Lillie: Brit. M. J. 2: 1111, 1960), 3 of the patients were noted to have epilepsy and to be receiving anticonvulsant drugs. Inasmuch as the incidence of epilepsy in patients at the particular hospital was only 1 in 400, a special relationship was suggested. Therefore the records of 44 epileptic patients who had 70 pregnancies were studied. In 7 (13 pregnancies) no anticonvulsant drugs were given and one instance of megaloblastic anemia occurred. In 48 pregnancies (28 patients) who were treated with phenobarbitone alone, no megaloblastic anemia was observed. However, in 7 pregnancies (7 patients) who were treated with both phenobarbitone and phenytoin 4 instances of megaloblastic anemia developed. One patient (one pregnancy) who received methoin alone did not develop anemia.

All of the anemias were severe and all responded promptly to the oral administration of 20 mg. of folic acid daily. This response occurred despite the continuance of the anticonvulsant therapy.

David M. Kydd

Editorial

The Australian and New Zealand Journal of Obstetrics and Gynaecology

ON MARCH 1, there appeared the first number of a new periodical for our Specialty, The Australian and New Zealand Journal of Obstetrics and Gynaecology. The event calls to our attention again the vitality and significance of Australian and New Zealand medicine and in particular the increasing maturity of obstetrics and gynecology in those still far-off lands.

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The new journal is sponsored jointly by three bodies, the Australian and the New Zealand Regional Councils and the Arthur Wilson Foundation. The two regional councils represent the fellows and members of the Royal College of Obstetricians and Gynaecologists of their respective dominions. These as a group include practically all the doctors specializing in obstetrics and gynecology in the area and comprise, as Fellows, 55 in Australia and 14 in New Zealand; as members, 203 in Australia and 46 in New Zealand. The Arthur Wilson Foundation has been set up in commemoration of a late distinguished obstetrician of Melbourne.

The new journal will be under the editorship of Dr. Eric Mackay of the Department of Obstetrics and Gynaecology of the University of Melbourne, with three associate editors, Professor J. W. Wright of Dunedin, New Zealand, Alan Grant of Sydney, and John Nattrass of Melbourne. A Board of Management, derived from the three sponsoring organizations, under the chairmanship of Professor Lance Townsend, will have the ultimate direction of the enterprise. An Editorial Committee composed of representatives of each of the 6 states of Australia and of New Zealand reminds one that it is not only in America that regional pride must be given due consideration.

Publication will at first be on a quarterly basis, "with a double column format and liberal illustrations." The table of contents of the first number offers a most promising list of interesting subjects. The Editors extend their heartiest best wishes for the success of The Australian and New Zealand Journal of Obstetrics and Gynaecology.

A. B. J. B. H. T. Item

American Board of Obstetrics and Gynecology

Applications for certification in the American Board of Obstetrics and Gynecology, new and reopened, for the 1962 Part I examinations are now being accepted. All candidates are urged to make such application at the earliest possible date. The deadline date for receipt of applications is Aug. 1, 1961. No applications can be accepted after that date.

Candidates for admission to the examinations are required to submit with their application a plain typewritten list of all patients admitted to the hospitals where they practice for the year preceding their application or the year prior to their request for reopening of their application.

This information is to be attested to by the Record Librarian of the hospital or hospitals and submitted on paper $8\frac{1}{2}$ by 11 inches. Necessary details to be contained in the list of admissions is outlined in the Bulletin and must be followed closely.

Current Bulletins outlining present requirements may be obtained by writing to the secretary's office.

All Diplomates of the Board are requested to inform the office of the secretary of a change in address.

Robert L. Faulkner, M.D. 2105 Adelbert Road Cleveland 6, Ohio



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Strain is a necessary component of man's efforts to move his external environment, but all too often brings on extreme pain and trauma when hard stools are moved after repair of rectal disorders. Metamucil adds soft, bland bulk to the bowel contents to stimulate normal peristalsis and also hold water within stools to keep them soft and easy to pass. Thus Metamucil, with an adequate water intake, is of great help in minimizing painful trauma to postsurgical rectal tissue. Metamucil promotes regularity through "smoothage" in all types of constipation.

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VISTARIL prepartum ...

allays apprehension and fear without impairing ability to cooperate during labor and delivery¹

reduces narcotic requirements and incidence of narcoticinduced respiratory depression; helps control nausea and vomiting; shortens stay in recovery room^{1,2}



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VISTARIL preoperatively...

allays anxiety and fear without depression of vital functions^{1,2}

permits substantial reduction in meperidine or other narcotics with rare incidence of hypotension, respiratory depression, or other untoward effects; relaxes skeletal muscle and smooths recovery; helps control emesis^{1,2}

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...and when administered postpartum or after surgery, VISTARIL maintains tranquility and helps control nausea and vomiting

IN BRIEF

VISTARIL Parenteral Solution is hydroxyzine hydrochloride.

Used preoperatively and postpartum, VISTARIL controls anxiety and fear, helps prevent emesis and smooths recovery. By reducing narcotic requirements substantially, VISTARIL helps to avoid narcotic-induced respiratory depression and hypotension. VISTARIL's calming effect usually does not impair discrimination, and is accompanied by direct and secondary muscle relaxation. No toxicity has been reported with VISTARIL, and it has a remarkable record of freedom from adverse reactions.

INDICATIONS: In addition to pre- and postpartum and pre- and postoperative tension and emesis, VISTARIL is clinically effective in other anxiety and tension states, senility, anxiety associated with various disease states, alcoholism, certain functional arrhythmias, and pediatric behavior problems.

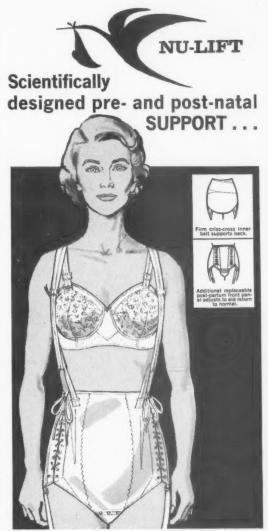
ADMINISTRATION AND DOSAGE: VISTARIL dosage varies with the state and response of each patient, rather than with weight, and should therefore be individualized by the physician for optimum results. The usual dosage in prepartum and preoperative sedation is 25-50 mg. I.M. or I.V. q. 4 h., p.r.n. Orally, up to 400 mg. per day in divided doses.

SIDE EFFECTS: Drowsiness may occur in some patients; if so, it is usually transitory, disappearing within a few days of continued therapy or upon reduction of dosage. Dryness of mouth may be encountered at higher doses.

PRECAUTIONS: The potentiating action of hydroxyzine should be taken into account when the drug is used in conjunction with central nervous system depressants. Do not exceed 1 cc. per minute I.V. Do not give over 100 mg. per dose I.V. Parenteral therapy is usually for 24-48 hours, except when, in the judgment of the physician, longer-term therapy by this route is desirable.

SUPPLIED: VISTARIL Parenteral Solution (hydroxyzine hydrochloride) – 10 cc. vials, 25 mg. per cc.; 2 cc. ampules, 50 mg. per cc. VISTARIL Capsules (hydroxyzine pamoate) –25, 50, and 100 mg. VISTARIL Oral Suspension (hydroxyzine pamoate) – 25 mg. per 5 cc. teaspoonful.

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Specific therapy for vaginal trichomoniasis VAGISEC® liquid and jelly. "Many other chemicals stop motion and we have assumed that the organisms are dead, but with [VAGISEC] there can be no doubt, since only fragments remain." 1

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Cure rates as high as 96% with VAGISEC confirmed by negative cultures for three consecutive months. Roberts and Sullivan³ successfully treated 96% (48 of 50) vaginal trichomoniasis patients with VAGISEC, all of whom remained flagellate free, as proved by repeated negative cultures for three months after treatment. Giorlando and Brandt,⁴ and Weiner⁵ were equally successful with VAGISEC, curing 93.1% (54 patients of 58), and 90.2% (46 patients of 51) respectively, by means of the VAGISEC technique.

To prevent re-infection—RAMSES® for the husband. As Romney® points out, "... therapy which is directed solely towards the female patient is unrealistic and ineffectual." Husbands readily cooperate when you prescribe RAMSES, the prophylactic with "built-in" sensitivity.

References: 1. Davis, C. H.: West. J. Surg. 63:53 (Feb.) 1955. 2. Decker, A.: New York J. Med. 57:2237 (July 1) 1957. 3. Roberts, C. L., and Sullivan, J. J.: West. Med. 1:12 (Apr.) 1960. 4. Giorlando, S. W., and Brandt, M. L.: Am. J. Obst. & Gynec. 76:666 (Sept.) 1958. 5. Weiner, H. H.: Clin. Med. 5:25 (Jan.) 1958. 6. Romney, S. L.: M. Sc. 8:235 (Aug. 25) 1960.

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*Active ingredients in Vagisec liquid: Polyoxyethylene nonyl phenol, sodium ethylene diamine tetra-acetate, sodium dioctyl sulfosuccinate. In addition, Vagisec jelly contains alcohol 5% by weight.

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1. Rosenfield, H. H., et al.: Obst. & Gynec. 11:222, 1958. 2. Bookmiller. M. M., and Bowen, G. L.: Textbook of Obstetrics and Obstetric Nursing, ed. 3, Philadelphia, Saunders. 1958. p. 314. 3. Hellman, L. D.: Gastroenterology.

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2. Palmer, A.: Internat. J. of Fertil. 4:365 1959



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Am. Pract. & Digest Treat., 10:461 (March) 1959.



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1. Simeckova, M.; Shaw, W.; Pool, E., and Nichols, E. E.: Numorphan in labor, Obst. & Gynec. 16:119, July, 1960. 2. Snow, D. L., and Sattenspiel, E.: A report on Numorphan in obstetrics, presented at the Congress of the Pan American Medical Association, Mexico City, May, 1960.

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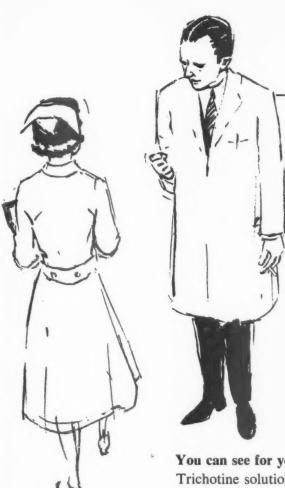


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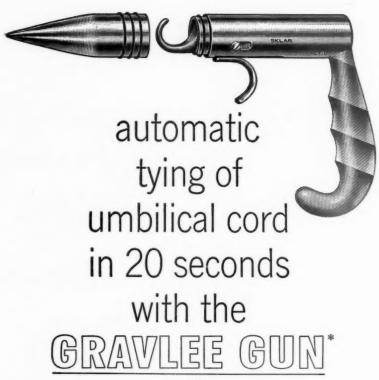
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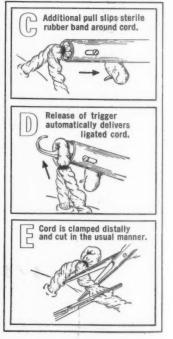


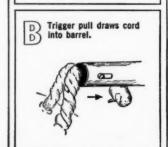
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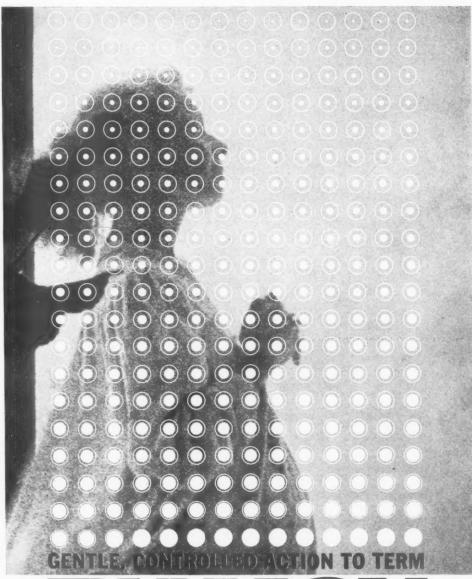
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Slack cord is looped over hook at desired distance from umbilicus.

1. Gravlee, L. C., and Jones, W. N.: Obst. & Gynec. 15:43 (Jan.) 1960. * U. S. PAT. NO. 2,942,604,



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1. Bayly, M. A., Desoxyephedrine As An Aid In Weight Control For Pregnant Clinic Patients, Quart. Bull. Northwestern Univ. M. School, 34:93, 1960.

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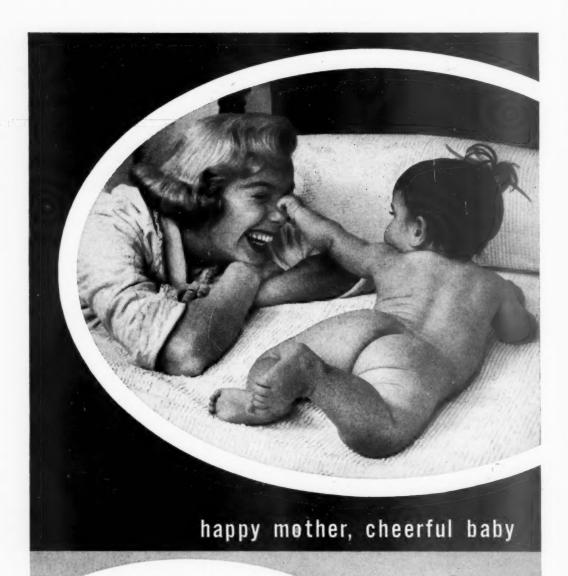
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Balances the mood-no "seesaw" effect of amphetamine-barbiturates and energizers. While amphetamines and energizers may stimulate the patient-they often aggravate anxiety and tension. And although amphetamine-barbiturate combinations may counteract excessive stimulation-they often deepen depression.

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Acts swiftly—the patient often feels better, sleeps better, within two or three days. Unlike most other antidepressant drugs, Deprol relieves the patient quickly—often within two or three days.

Acts safely - no psychotic reactions.

Deprol does not cause hypotension, tachycardia, jitteriness, or liver toxicity. It can be safely administered with basic therapy.

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Smooth, easy-to-clean finish. May be sterilized with alcohol, soap solution, common cleaning compounds. (Model for hospital use is fully autoclavable.)

Keeps body weight off perineal areas.

Patient is in a normal relaxed sitting position. Simple valve directs water so patient can fill or drain the bath, or maintain proper water temperature for soaking without getting up. Gentle swirling motion of water may be maintained.

REG-U-TEMP



Although relatively little water is required for the REG-U-TEMP, perineal areas are completely immersed.

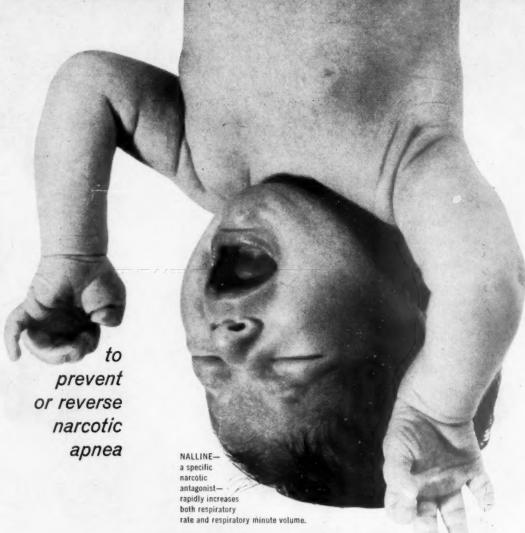
Used at leading hospitals.

Thousands of REG-U-TEMP sitz baths are already available to hospital patients. Mail the coupon for distributor's name and a demonstration.

Harlan M. Buck, Inc., Box 237, Rye, N.Y.

Please send me the name of the distributor nearest me who handles REG-U-TEMP, and arrange to have someone show me a REG-U-TEMP at my office.

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INJECTION

Nalline

HYDROCHLORIDE

NALORPHINE HYDROCHLORIDE INJECTION, U.S.P.

Maximal safety in obstetric procedures requiring narcotics is promoted by the routine availability in the delivery room of the narcotic antagonist NALLINE. Injected five to fifteen minutes before delivery in the mother suffering from moderate or severe narcotic-induced respiratory depression, NALLINE combats the maternal depression and reduces the risk of narcotic apnea in the newborn infant. For active management of asphyxia neonatorum, NALLINE is injected into the infant, as a means of directly antagonizing the narcotic effect and thus decreasing the need for stressful resuscitation.

Supplied: For adult use only (5 mg. per cc.), ampuls of 1 and 2 cc.; vials of 10 cc. For neonatal use (0.2 mg. per cc.), ampuls of 1 cc. WARNING: May be habit-forming. NOTICE: Subject to the Federal Narcotic Law. Additional information on NALLINE is available to physicians on request. NALLINE is a trademark of Merck & Co., INc.



MERCK SHARP & DOHME Division of Merck & Co., Inc., West Point, Pa.

Capillary protective measures in pregnancy

Prenatal treatment and threatened abortion

During pregnancy, fragile capillaries, increased capillary permeability, decidual bleeding, and the tendency toward edema are well recognized. Essential capillary protective factors are an integral part of the prenatal regimen.

The inclusion of Hesperidin or other citrus bioflavonoids as a "precautionary measure" in every pregnancy and as an "essential measure" in habitual aborters insures the restoration and maintenance of capillary integrity and helps prevent spontaneous abortion.

The rationale of Hespiridin and other citrus bioflavonoids—in conjunction with vitamin C, nutritional factors and other therapeutic measures—as adjuncts, is based on the premise that capillary involvement may be a contributing factor in spontaneous abortion and erythroblastosis fetalis.

Hesperidin, Lemon Bioflavonoid Complex and their naturally occurring synergist ascorbic acid are readily available capillary protective factors for the restoration and maintenance of capillary integrity and function.

Sunkist Growers PHARMACEUTICAL DIVISION • ONTARIO, CALIFORNIA Specialty formulations produced by the leading pharmaceutical manufacturers contain Sunkist® brand Hesperidins and Lemon Bioflavonoid Complex.

in induction and stimulation of labor-method of choice

PIPOCIN

"Intravenous PITOCIN may be used successfully in elective or indicated inductions of labor. It has a definite place in the stimulation of labor in the early part or later stages either in desultory preliminary labor, or in primary or secondary uterine inertia."*

PITOCIN (oxytocin injection, Parke-Davis) is supplied in 0.5-cc. (5-unit) ampoules, in boxes of 10 and in 1-cc. (10-unit) ampoules, in boxes of 10. Each cc. contains 10 international oxytocic units (U.S.P. units). See medical brochure for details of administration and dosage.

*Fields, H.; Greene, J. W., Jr., & Franklin, R. R.: Obst. & Gynec. 13:353, 1959. 22761 PARK

PARKE DAVIS & COMPANY Detroit 12 Michigan







penetrates the monilial membrane

non-staining, potent vaginal monilicide

SPOROSTACIN CREAM

Unique molecular structure of active agent facilitates penetration of the monilial membrane for exceptional fungicidal activity and outstanding clinical benefits.1.4

- = rapid relief of symptoms usually within 2 days, often within hours
- high percentage of culture-proved cures
- single course of treatment usually adequate
- white, soothing and odorless
- enthusiastically accepted by patients

- Lapan, B.: Am. J. Obst. & Gynec., 78:1320, 1959. (156 patients)
 Breen, J. L.: Obst. & Gynec., to be published. (39 patients)
 Nathanson, E. A.: Obst. & Gynec., 16:601, 1960. (100 patients)
 Mendel, E. B.: Am. J. Obst. & Gynec., to be published. (109 patients)





TRIMAGILI

POWDER-VAGINAL INSERTS

- a new, rational, convenient therapy for
 - Trichomonas vaginalis
 - · Candida albicans (Monilia)
 - Hemophilus vaginalis
 - Non-specific leukorrhea

WHAT IS TRIMAGILL?

Trimagill is presented as a powder for insufflation and as dry, nongreasy vaginal inserts containing Tartaric Acid, Citric Acid, Dextrose, Boric Acid, Potassium Bitartrate, Potassium Alum, and Adhesives.

TRIMAGILL IS LOGICAL!

Pathogenic micro-organisms that cause vaginal infections are incapable of surviving or propagating in a low pH environment. Trimagill produces and maintains a vaginal pH of 2.0 to 2.5—thus, infecting organisms are destroyed because an unfavorable environment is created.

TRIMAGILL IS EFFECTIVE!

Trimagill's low pH favors the growth of beneficial Döderlein bacilli and helps restore vaginal flora following infections. Unlike antibiotics Trimagill does not foster monilia overgrowth.

TRIMAGILL IS PRACTICAL AND CONVENIENT!

Trimagill Powder adheres to the vaginal mucosa for several hours -eliminates need for vaginal and introital packs or external pads. Trimagill Powder is easily applied during office visits; Trimagill Vaginal Inserts are recommended for patient use between office visits.

UNINTERRUPTED MEDICATION!

Trimagill treatment may safely be continued during menstruation thus preventing the normal physiological change from an acid to an alkaline pH.

TRIMAGILL IS SAFE!

No untoward reactions have been reported in over 3,000 cases treated to date. The combination of ingredients in Trimagill produces an unusually low pH with emollient properties that prevent irritation of mucous membranes.

TRIMAGILL IS PROVED BY CLINICAL EXPERIENCE!

Published paperst representing years of clinical experience in over 3,000 patients demonstrate the effectiveness and safety of Trimagill. Trimagill was used successfully in these cases primarily for acidification of the vaginal tract in treatment of vaginal infections. It was also used and is recommended as a non-absorbable agent following conization of the cervix to help eliminate postoperative sloughing, perineal odor, absorb secretion and maintain an acid pH.

TRIMAGILL IS SUPPLIED:

As Powder: 5 oz. Plastic Insufflator Bottles; As Vaginal Inserts: Boxes of 24. NOTE: Consult package circular for full details on instructions for use of both Powder and Vaginal Inserts.

WRITE FOR SAMPLES AND REPRINTS

*Patent Applied For.

†Reprints of published papers available on request.



THE S. E. ASSENGILL COMPANY
Bristol, Tennessee

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female adolescence-a period of confusion

Confusion twice confounded surrounds the young girl during puberty. Surely this transition — rapid and in many ways still mysterious — deserves your special counseling. When your advice includes the use of Tampax® — the modern tampon method of protection — you are offering your patient, in addition, the reassurance of safe, complete, discreet menstrual hygiene.

of safe, complete, discreet menstrual hygiene.
Tampax is frictionless and nonirritating. It will not cause erosion or block the menstrual flow. Because Tampax provides internal protection, it does not favor the development of odor or establish a bridge for the entry of pathogenic bacteria. Tampax does afford easy management, easy disposal. And since wide clinical

evidence confirms that virginity is not a contraindication to its use, Tampax is suitable for every age of the menstrual span. Youngsters especially appreciate Tampax at gym and swim time. There are no encumbrances to interfere with activity or to cause embarrassment. The older girl favors Tampax because of the social poise it makes possible, despite "the time of the month." Tampax is available in three absorbencies to meet varying requirements.

Why not suggest "Tampax" to your teenage patients? Its matter-of-fact simplicity, safety and security are outstanding features — sure to be welcome now and in the years ahead.

Tampax Incorporated, Palmer, Mass.

first first first

the first practical answer to symbiotic therapy of vaginitis with Döderlein Bacilli...new

Dödercil®

Döderlein Bacilli, Wynlit

The use of Döderlein Bacilli in the management of vaginitis has been a goal of more than half a century of research; this biological approach to therapy is now available as Dödercil, truly a triumph in research and production.

- special, pure, dominating strain of viable Döderlein Bacillus with great proclivity for survival
- a stable lyophilized powder of assured bacterial count
- for vaginal instillation powder is reconstituted as a suspension

- a course of vaginal instillations
 - restores normal flora
 - restores normal pH
 - -rapidly alleviates symptoms
 - -rapidly clears clinical signs

Orders shipped direct from Madison; literature and prices available upon request.



WYNLIT PHARMACEUTICALS, INC. Madison, New Jersey

May, 1961

Page 111



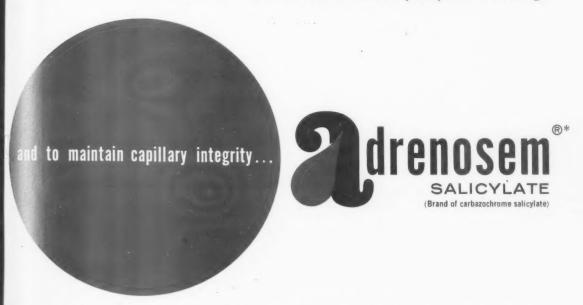
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Briste

Holding blood loss to a minimum is a medical precept. Clinical studies show that lack of capillary integrity causes abnormal bleeding four times as often as coagulation defects.^{1,2}

Adrenosem aids capillary integrity by decreasing excessive capillary permeability and promoting retraction of severed capillary ends.

Adrenosem protects against bleeding from PREOPERATIVELY small vessels, thus assuring a clearer operative field and minimizing the need for transfusions.

POSTOPERATIVELY Adrenosem reduces postoperative bleeding.



Used nonsurgically, Adrenosem controls internal bleeding associated with vascular pathosis, as in peptic ulcer, telangiectasia, purpura, ecchymosis, ulcerative colitis, and others.

Contraindications: None at recommended dosage levels—seven years' clinical use, over 15 million doses, and over 35 published studies prove the safety and effectiveness of Adrenosem.

Supplied: Ampuls, 5 mg. (1 cc.) and 10 mg. (2 cc.) for I.M. injection; Tablets, 1 and 2.5 mg.; Syrup, 2.5 mg./5 cc. (1 tsp.)

- 1. Haden, R.L., et al.: Ann. N.Y. Acad. Sc. 49:641 (May 11) 1948.
- 2. Cheraskin, E.: J. Am. Dent. Assn. 58:17 (April) 1959.
- *U.S. Pat. Nos. 2581850; 2506294

write for detailed literature

THE MASSENGILL COMPANY

Bristol, Tennessee

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In Iron Deficiency Anemias

IROMIN-G

WANTED-Full-time associate in Obstetrics and Gynecology; 317 bed general teaching hospital and large diagnostic clinic located in the East. New Obstetrics wing now under construction. All departments adequately staffed by full-time Board certified M.D.'s and Ph.D.'s. Please give full summary of qualifications when answering. Reply to Box AM, American Journal of Obstetrics and Gynecology, 3207 Washington Blvd., St. Louis 3, Missouri.



FOR RAPID HEMOGLOBIN RESPONSE

IROMIN-G® tablets contain, in addition to the well tolerated ferrous gluconate, copper and manganese for rapid hemoglobin regeneration, and a complete nutritional supplement of the essential minerals and vitamins including Vitamin B-12.

Results are usually achieved without gastric upset, constipa-

tion or diarrhea.

INDICATIONS: Secondary anemias and as a supplement for the prenatal, teen-age, and aeriatric diet.

SUPPLIED: Bottles of 100 DOSAGE: One tablet three times a day after meals or as directed by a physician.

The suggested daily schedule provides:

Ferrous Gluconate	1000.0	mg
(Iron	116.0	mg)
Vitamin B ₁₂ (crystalline, on resin)	6.0	mcgm
Ascorbic Acid (Vitamin C)	120.0	mg
Vitamin A Acetate1500	0.0 US	P units
Vitamin D ₂ 150	0.0 US	P units
Thiamine Mononitrate (Vitamin B ₁)	6.0	mg
Riboflavin (Vitamin B ₂)	6.0	mg
Pyridoxine Hcl (Vitamin B _b)	3.0	mg
d-Calcium Pantothenate (Vitamin B ₅)	3.0	mg
Niacinamide (Vitamin B ₁)	60.0	mg
Calcium Lactate	576.0	mg
Calcium Carbonate	210.0	mg
(Calcium	159.0	mg)
Copper (as Sulfate)	0.45	5 mg
Manganese (as Citrate soluble)	0.75	5 mg
Zinc (as Oxide)	0.24	4 mg
Potassium (as Chloride)	15.0	mg
Magnesium (as Carbonate)	7.5	ma

COMPLETE LITERATURE AND SAMPLES ON REQUEST

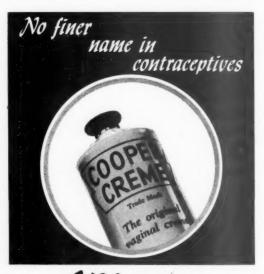


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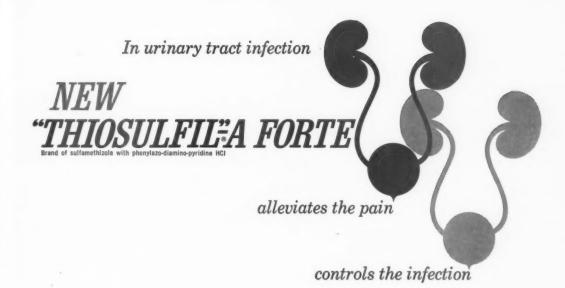
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WHITTAKER LABORATORIES, INC., PEEKSKILL, NEW YORK



"THIOSULFIL"-A FORTE combines the sulfonamide specific for urinary tract infection with a potent analgesic for prompt, soothing relief of local discomfort.

Recommended in acute urinary tract infection, such as cystitis, urethritis, pyelitis, pyelonephritis, and prostatitis due to bacterial infection amenable to sulfonamide therapy. "Thiosulfil" has been effective against the following urinary pathogens: Proteus vulgaris, Pseudomonas aeruginosa, Escherichia coli, Streptococcus fecalis, Escherichia intermedium, and Aerobacter aerogenes. In individual cases, sensitivity of the organisms may vary. Sensitivity tests, preferably by the tube dilution method, should be done first, for guidance as to alternate therapy in case "Thiosulfil"-A Forte does not control the infection.

USUAL DOSAGE: Adults: 2 tablets, four times daily.

Children: (9 to 12 years): 1 tablet, four times daily.

WARNING: Due to the high solubility in body fluids of "Thiosulfil" and its acetyl form, the hazards of renal tubule obstruction are minimized. The usual precautions exercised with sulfa drugs generally should, however, be observed. In those rare instances where exanthemata, urticaria, nausea, emesis, fever or hematuria, are encountered, administration should be discontinued.

CONTRAINDICATIONS: (1) a history of sulfonamide sensitivity and (2) due to the phenylazodiamino-pyridine HCl component, renal and hepatic failure, glomerulonephritis, and pyelonephritis of pregnancy with gastrointestinal disturbances.

SUPPLIED: "Thiosulfil"-A/Forte-No. 783: Each tablet contains sulfamethizole 0.5 Gm., and phenylazo-diamino-pyridine HCl 50.0 mg., in bottles of 100 and 1,000.

also available: "Thiosulfil"-A-No 784: Each tablet contains sulfamethizole 0.25 Gm., and phenylazo-diamino-pyridine HCl 50.0 mg., in bottles of 100 and 1,000.

USUAL DOSAGE: Adults: 2 tablets, four times daily. Children: (9 to 12 years): 1 tablet, four times daily.

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One pharmaceutical research executive points up the importance of failures as guideposts to success in the search for new or improved drugs when he says:

"Failure is our most important product."

The pharmaceutical industry's investment in research has been growing much faster than the industry itself. Last year the prescription drug companies spent a record \$197 million for research, a five-fold increase in the space of ten years. Such an investment is possible, of course, only when there are profits. • This growth in privately financed research has sent the volume of laboratory failures soaring. For two years in a row the pharmaceutical industry has tested more than 100,000 substances in the search for new medicines. Fewer than two per cent showed enough promise for clinical testing. Only a handful will ever be sold as prescription drugs. The odds against finding a product with therapeutic value probably exceeded 2000to-1. • But year by year, as the failures mount, the successes also increase, putting new or improved medications at the disposal of the medical profession. And the public benefits through better health, specific cures, shorter hospitalization, longer lives. • This is only one part of the massive assault on disease that engages the health team headed by the medical profession and embracing hospitals, nurses, pharmacists, technicians, and colleges. It is an effort that could only take place in a society which encourages individual

freedom and guarantees incentives to freedom of enterprise.

This message is brought to you in behalf of the producers of prescription drugs. For additional information, please write Pharmaceutical Manufacturers Association, 1411 K Street, N.W., Washington 5, D. C.

for pre- and postnatal lower urinary tract infections consider the safety and efficacy of

MANDELAMINE

the urine-specific antibacterial

Mandelamine's demonstrated safety makes it the ideal drug to eliminate lower urinary tract infections complicating pregnancy or the puerperium. By its antibacterial action in the urine, Mandelamine also helps prevent ascending pyelonephritis.

Urine-specific Mandelamine destroys most urinary pathogens (including many strains resistant to antibiotics and sulfonamides) without producing resistant mutants. Sensitization and superinfections do not occur after prolonged use, and Mandelamine is economical therapy.

Dosage: Adults—Two Mandelamine Hafgrams four times a day. Precautions: Mandelamine is contraindicated in patients with renal insufficiency and/or severe hepatitis. An occasional patient may experience gastrointestinal disturbance. Supplied: Mandelamine Hafgram® tablets (0.5 Gm.), and pleasantly flavored Mandelamine Suspension.



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Full dosage information, available on request, should be consulted before initiating therapy.

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GP13





Put your low-back patient back on the payroll

Soma's prompt relief of pain and stiffness can get your low-back patients back to work in days instead of weeks

Soma is unique because it combines the properties of an effective muscle relaxant and an independent analgesic in a single drug. Unlike most other muscle relaxants, which can only relax muscle tension, Soma attacks both phases of the pain-spasm cycle at the same time.

Thus with Soma, you can break up both

pain and spasm fast, effectively . . give your patient the two things he wan most: relief from pain and rapid return full activity.

Soma is notably safe. Side effects are rar Drowsiness may occur, but usually only wil higher dosages. Soma is available in 350 m tablets. Usual dosage is 1 tablet q.i.d.

The muscle relaxant with an independent pain-relieving action





W Wallace Laboratories, Cranbury, New Jersey





WHITE COTTON GOWNS 48" Long-O.K. for X-Ray

#2G—Crinkle Cloth requires NO IRONING

COLOR of TIES tells SIZE ____Size 1 small (blue ties)—42" ____Size 2 medium (white ties)—52"

2 is best size ____Size 3 large (pink ties)—60"

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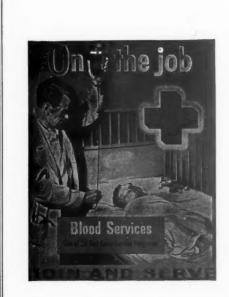
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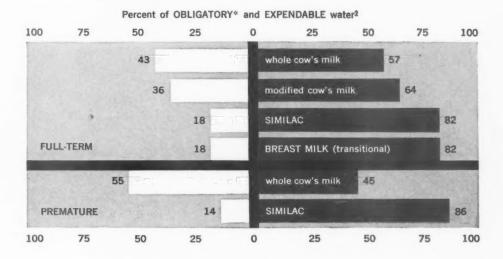
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 physiologic protection for infants—with SIMILAC®

"The osmolar load is an important factor in infant feeding since the kidneys can excrete a urine of only a limited osmolar concentration.... In addition to producing good nutrition under conditions with low extrarenal losses of water, milk mixtures must be appropriate for infants requiring high extrarenal losses of water."

In young infants under normal conditions, the average renal solute concentration from whole cow milk formulas may be more than twice the concentration from Similac, a low osmolar feeding.² But in the presence of high environmental temperatures and in conditions causing heat stress and body water loss, the urinary osmolar concentration may be expected to reach a maximum. The consequent decrease in expendable water for renal excretion may then cause undue demands to be made on body water for the renal excretion of the end products of whole cow milk formulas.^{1,3}

The results of a recent study2: with 42 full term and 7 premature infants

"There was a larger amount of unobligated or expendable renal water in the infants fed the [Similac] than in those fed whole cow's milk . . . the margin of safety with [a whole cow milk formula] with regard to water requirements would be greatly reduced when extrarenal water losses are excessive." 2



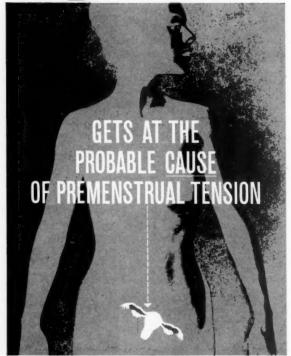
*"Among young infants there is a variability in the capacity of the kidney to excrete a solute load at a given rate and concentration....[Although] it is known...that some full-term newborn infants and older premature infants may concentrate to much higher levels..., for the purposes of this study, it is assumed to be 700 mOsm per liter."

PERCENTAGES OF OBLIGATORY AND EXPENDABLE RENAL WATER DEMONSTRATE STILL FURTHER THE PHYSIOLOGIC SIMILARITY BETWEEN BREAST MILK AND SIMILAC: there is no closer nutritional equivalent to the milk of healthy, well-nourished mothers.

References: 1. Darrow, D. C., et al.: Pediatrics 14:602 (Dec.) 1954. 2. Calcagno, P. L., and Rubin, M. I.: J. Pediat. 56:717 (June) 1960. 3. Committee on Nutrition, American Academy of Pediatrics: Pediatrics 19:339 (Feb.) 1957.

ROSS LABORATORIES Columbus 16, Ohio

Cytran



to restore hormonal balance...

corrective therapy Because Cytran contains the new progestin, Provera*, you can now reach the probable cause of premenstrual tension—hormonal imbalance. The estrogen-progesterone ratio is adjusted to more normal premenstrual balance. Abdominal discomfort, shakiness, fatigue—symptoms incompletely controlled by mere symptomatic treatments—are often effectively relieved.

to comfort the patient...

SYMPTOMATIC THERAPY An effective diuretic (Cardrase*) and a mild tranquilizer (Levanil*) afford symptomatic relief during the time required to effect basic correction. They also supplement the activity of Provera in those patients in whom restoration of hormone balance does not completely eliminate edema and anxiety/tension.

Each tablet contains:

Lacii tabiet contains.		
Provera (medroxyprogesterone acetate)	2.5	mg.
Cardrase (ethoxzolamide)	35	mg.
Levanil (ectylurea)	300	mg.

Usual dosage: 1 to 2 tablets daily, 5-10 days before the period.

Supplied: As layered tablets in bottles of 20 and 100.

Precautions: Side effects following the use of Cytran are rare. The patient should be observed for possible sensitivity to one or more of the components. Drowsiness, if seen, may be relieved by decreasing the dosage.

Contraindications: Cýtran should not be used in patients with abnormal uterine bleeding until malignancy and all other organic pathologic conditions have been ruled out. Carbonic anhydrase inhibitors should not be administered in the presence of renal failure, hyperchloremic acidosis, Addison's disease, or any condition involving depressed sodium and/or potassium levels. Caution must be observed in the presence of symptomatic hepatic cirrhosis as acidosis may develop. Tranquilizing agents, generally, are not indicated in true depressive states without concomitant anxiety.

TTRADEMARK

*TRADEMARK, REG. U.S. PAT. OFF.

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THE UPJOHN COMPANY # KALAMAZOO, MICHIGAN



antibacterial, antimonilial, antitrichomonal effects—optimal dispersion, prolonged retention

85% success: 1,2 Triburon Chloride — the clinically proven microbicide — provides rapid symptomatic relief as well as control of trichomonal, monilial and non-specific vaginitis. In one study,1 discharge, itching and burning disappeared in 67 of 73 women after only 3 or 4 applications; after two weeks, cultures were negative in 61 patients. Similar results were noted in another series of 55 women.2

now available in two forms

New TRIB VAGINAL SUPPOSITORIES provide the efficacy of Triburon Chloride in a water-soluble, self-emulsifying base that enhances dispersion and prolongs therapeutic effects, even in the presence of profuse discharge. TRIB VAGINAL SUPPOSITORIES are provided with reusable plastic applicators.

Proven TRIB VAGINAL CREAM—white, nonstaining, virtually non-irritating to the vaginal mucosa, with no hint of medicinal odor. Disposable applicators are supplied with the cream.

ndications: TRIB VAGINAL SUPPOSITORIES and TRIB VAGINAL CREAM for vulvitis and vaginitis due to Trichomonas vaginalis, Candida albicans, Hemophilus vaginalis as well as mixed infections; after cauterization, conization and irradiation, for surgical and postpartum treatment. Therapy may be continued during pregnancy and menstruation.

Supplied: TRIB VAGINAL SUPPOSITORIES—Boxes of 24, with reusable applicator. TRIB VAGINAL CREAM - 3-ounce tubes with 18 disposable applicators. Consult literature for dosage requirements, available on request, before prescribing.

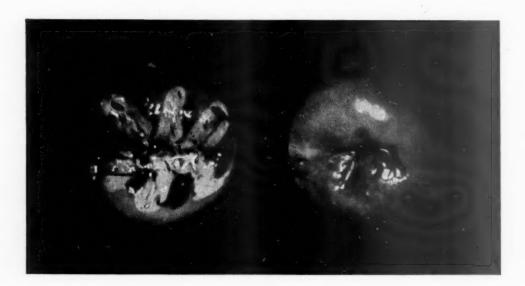
contains Triburon Chloride 0.1%

Vaginal Cream & Suppositories

FORMERLY TRIBURON VAGINAL CREAM decisive microbicidal therapy in a delicate matter not an antibiotic . not a nitrofuran



References: 1. N. Mulla and J. J. McDonough, Ann. New York Acad. Sc., 82: (Art. 1), 182, 1959. 2, L. E. Savel, Division of Hoffmann-LaRoche inc. D. B. Gershenfeld, J. Finkel and P. Drucker, ibid., p. 186.



For your OB-GYN patients: fight infection, facilitate healing

Administered before and after cervicovaginal surgery, irradiation, delivery, and office procedures such as cauterization, Furacin helps to provide a shorter, more comfortable convalescence. Infection is promptly controlled; discharge, irritation and malodor reduced; healing hastened. Furacin is highly active in the presence of exudates, yet is nontoxic to regenerating tissue, does not induce significant bacterial resistance nor encourage monilial overgrowth.

FURACIN



Vaginal Suppositories

FURACIN 0.3% in a water-miscible base which melts at body temperature. Box of 12, each 2 Gm. suppository hermetically sealed in yellow foil.

Cream

FURACIN 0.2% in a fine cream base, water-miscible and self-emulsifying in body fluids. Tubes of 3 oz., with plastic plunger-type vaginal applicator.

THE NITROFURANS—
a unique class of antimicrobials
EATON LABORATORIES, NORWICH, NEW YORK



longer-acting, fewer injections for fetal salvage with no androgenic effect

DELALUTIN

Delalutin offers these advantages over other progestational agents: Significantly improved rate of fetal salvage¹⁻³ No virilizing effect on female fetus or mother High, sustained hormonal level in the uterine muscle and mucosa⁴—high enough

even to replace an excised corpus luteum5

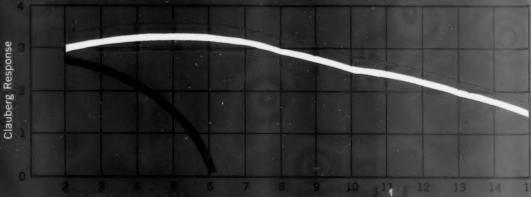
■ Absence of local tissue reactions³.

Comparative effect of single subcutaneous injection of Detalution and progesterone on the progestational changes [Clauberg Test] in the rabbit utarus.

Borman, A.: Laboratory Report on the Ourstien of Action of 17. Alpha-Hydroxy-progesterone-n-Caprocts (Delaiutie). The Squibt Institute for Medical Research, May 17, 1955.

Hydroxyprogesterone Caproate (Delalutin)

Rrogesterone



Days following injection

Supply: Vials of 2 and 10 cc., each oc. containing 125 mg. of hydroxyprogesterone caprosts in sessme oil with 35% benzyl benzasts. Vials o 5 cc., each oc. containing 250 mg. of hydroxyprogesterone caprosts in castor oil with 51% benzyl benzasts. References 1. Boschann, H. W. Ann. New York Acad. Sc. 71:727 (July 30) 1955. 3, Castelann Ayels, L. et al., Gin. y Obstot. co shortes 14:290 (Mg. Juny) 1955. 4, Plotz, E. J.: Abortion (Hamorrhoge of Early Programmy), in Conn. H. F.: Curren Therapy – 1950, Philledsiphia: W. S. Seunders Co., 1955, pp. 613 ff. 5. Wright, H. L., Wilhers, R. W., and Ingram, J. Mill Am. Pract. & Diges Treet, 19154, (Seath 1956).

Complete information on administration and decays is expelled in the

SQUIBB

Squibb Quality—the Priceless Ingredient

Because its components are not precursors, but active enzymes, ELASE quickly lyses fibrinous material in serum, clotted blood, and purulent exudates. It does not appreciably attack living tissue, nor have an irritating effect on granulation tissue in wounds.1-4 ELASE is useful in vaginitis and cervicitis, and as adjunctive treatment in cervical erosion...surgical wounds...burns...chronic skin ulcerations...infected wounds ...fistulas...sinus tracts...abscesses...and ulcerative lesions of various types.

Provides Prompt Sympto-

matic Relief.
In one series
of 129 patients with
cervical
pathol-

ogy of various kinds, including nonspecific cervicitis, erosions, lacerations, postpartum cervicitis, and postelectrocauterization lesions, the use of ELASE was followed by complete healing in 69 per cent of cases, and partial healing in 20 per cent. Following electroconization of the cervix, ELASE helps to eliminate the postconization cervical plug, thus minimizing the danger of hemorrhage following discharge of the plug.

See medical brochure for details of administration and dosage.

PACKAGE INFORMATION: ELASE Ointment is supplied in 10-Gm. and 30-Gm. tubes. Disposable vaginal applicators (V-Applicators) for instillation of ointment are available separately in packages of 6. ELASE is also supplied in rubber-diaphragm-capped vials of 30-cc. capacity for reconstitution with 10 cc. of isotonic sodium chloride solution.

REFERENCES: (1) Coon. W. W.; Wolfman, E. F., Jr.; Foote, J. A., & Hodgson, P. E.: Am. J. Surg. 98:4, 1959. (2) Friedman, E. A.; Little, W. A., & Sachtleben, M. R.; Am. J. Obst. & Gynec. 79:474, 1960. (3) Margulis, R. R., & Brush, B. E.: Arch. Surg. 65:511, 1952. (4) Personal Communications to the Department of Clinical Investigation, Parke, Davis & Company, 1959.

or
enzymatic
debridement
in certain
gynecologic
complications

FIBRINOLYSIN
to provide <u>active</u>
enzyme for lysis
of fibrin +

DESOXYRIBONUCLEASE
to lyse desoxyribonucleic acid in
degenerating
leukocytes and other
nuclear debris

PARKE-DAVIS

PARKE, DAVIS & COMPANY, Detroit 32, Michiga

consider
the convenience
to pregnant
women of
a tablet this size



FIGRA NEW FORMULA SUPPLIES 45 MG. OF IRON—AT NO EXTRA COST

The size of a prenatal vitamin-supplement tablet is important—the nausea and gastric distress often associated with pregnancy may make swallowing anything a real problem.

Hence the small size of the Engran tablet is a great convenience to your pregnant patient, for Engran is actually the *smallest* tablet now available for vitamin-mineral supplementation.

Yet only one Engran tablet a day will provide these vitamins and minerals to help assure a nutritionally perfect pregnancy: vitamin A 5,000 U.S.P. units; vitamin D 500 U.S.P. units; vitamin K 0.5 mg.; thiamine 3 mg.; riboflavin 3 mg.; pyridoxine 2 mg.; vitamin B_{12} 2 mcg.; niacinamide 20 mg.; calcium pantothenate 5 mg.; ascorbic acid 75 mg.; calcium 100 mg.; iron 45 mg.; iodine 0.15 mg.; copper 1 mg.; magnesium (as the oxide) 6 mg.; zinc 1.5 mg.; manganese (as the sulfate) 1 mg.

For full information see your Squibb Product Reference or Product Brief.

SQUIBB I

BO

uncomplicated

prevention of "next-morning sickness" with a single bedtime dose

Bonine®

BRAND OF MECLIZINE HYDROCHLORIDE

a record of effectiveness, excellent toleration, and economy



IN BRIEF

BONINE (meelizine hydrochloride) is the dihydrochloride of 1-p-chlorobenzhydryl-t-m-methylbenzylpiperazine, an antihistaminic-anticholinergic compound for prevention and relief of nausea and vomiting due to a variety of causes.

NDICATIONS: Valuable in the symptomatic relief of nausea and vomiting of pregnancy. Also indicated for motion sickness, radiation sickness,

certigo associated with Ménière's syndrome, labyrinlitis, fenestration procedures, vestibular dysfunction, and izziness associated with cerebral arteriosclerosis.

ADMINISTRATION AND DOSAGE: For control of nausea and comiting of pregnancy, a single dose of 25 to 50 mg. at hedtime is usually effective. For dosage schedules in other indications, see package insert.

SIDE EFFECTS: Not a phenothiazine, the side effects reported in association with BONINE have been uncompli-

cated, mild and/or transient and consist of occasional drowsiness, dryness of the mouth, and blurred vision. There are no known contraindications to BONINE.

PRECAUTIONS: As with other antihistaminic compounds, the physician should inform patients of the need for caution in driving a car or when engaged in other activities requiring alertness.

SUPPLIED: BONINE Tablets, scored, tasteless, 25 mg.
BONINE Chewing Tablets, mint-flavored,
25 mg. BONINE Elixir, cherry-flavored,
12.5 mg. per teaspoonful (5 cc.).

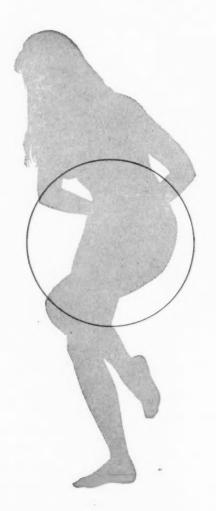
only rarely does one drug meet so well the needs of one condition

More detailed professional information available on request.

PFIZER LABORATORIES Division, Chas. Pfizer & Co., Inc. Brooklyn 6, N.Y. / Science for the world's well-being"



in female urethritis referred pain complicates diagnosis



Pain in the groin, suprapubic region, thighs and lower back is often caused by urethritis but, as a result of negative urinary findings, is attributed to other organs. Direct examination of the urethra helps localize the origin of referred pain, evidence of urethral inflammation. calling for local therapy.

Younger women with bacterial urethritis respond to the antibacterial, anesthetic and dilating effects of FURACIN Inserts (formerly FURACIN Urethral Suppositories) containing nitrofurazone 0.2% and the local anesthetic diperodon HCl 2% in a water-dispersible base. Each suppository hermetically sealed in silver foil, box of 12.

Older women respond to the estrogenic, antibacterial, anesthetic and dilating effects of FURESTROL Suppositories containing, in addition to nitrofurazone and diperodon •HCl, diethylstilbestrol 0.0077% (0.1 mg.) which corrects postmenopausal urethritis at the cellular level. Each suppository hermetically sealed in orchid foil, box of 12.

FURACIN® INSERTS and brand of nitrofurazone FURESTROL® SUPPOSITORIES alleviate pain—simplify treatment

EATON LABORATORIES, NORWICH, NEW YORK



the critical fibrinogen index in 60 seconds



rtho Pharmaceutical Corporation



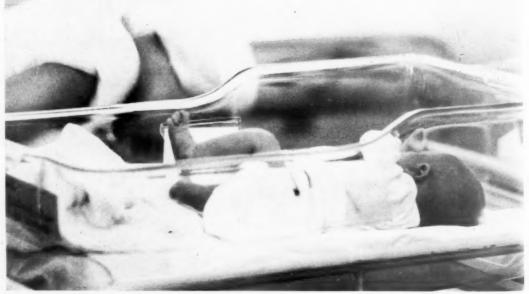
Why do 86% of pediatricians prefer evaporated milk for formula feeding?

Proven nutritional value!

Readily diluted and supplemented for the infant's changing needs, the evaporated milk formula fulfills the nutritional requirements of most infants from birth throughout infancy. A proven history of successful feeding makes evaporated milk the most widely used form of milk for infant feeding today.

Carnation's position of responsibility and leadership in the specialized field of infant feeding is important in the choice of formula milks. This is the milk used in more hospital formula rooms throughout the world than all other brands combined.

- Permits the doctor to prescribe for the baby's changing needs
- · Curd tension zero
- · Digestible, uniform, safe
- · Low incidence of allergy
- · Simple to prepare





WORLD'S LEADER BY FAR, FOR INFANT FORMULA FEEDING

"from Contented Cows"

THE READY-PREPARED EVAPORATED MILK FORMULA Carnalac is Carnation Evaporated Milk with its added Vitamin D, plus carbohydrate. The mother just adds water. Diluted 1:1, Carnalac provides 20 calories per fluid ounce.







full term fetus

complication:

threatened abortion

indicated:

rovera

Here are five reasons why:

- · Provera is the only commercially-available oral progestational agent that will maintain pregnancy in critical tests in ovariectomized
- · It is four times as potent (by castrate assay) as any other progestational agent.
- · No significant side effects have been encountered.
- · It is available for both oral and parenteral administration
- · Provera gives the economy of effective action from small doses.

Brief Basic Information

- I.M.

Oral Provers* D	
Oral Provera* D	epo-Provera**

	W Olai Floveia	Deho-1 104cla
Description	Upjohn brand of medroxy- progesterone acetate.	Aqueous suspension, 50 mg. Provera per cc., for intramuscu- lar injection only.
Indications	Threatened and habitual abortion, infertility, dysmenorrhea, secondary amenorrhea, premenstrual tension, functional uterine bleeding.	Threatened and ha- bitual abortion, en- dometriosis.
Dosage Threatened abortion	10 to 30 mg, daily until acute symptoms subside.	50 mg. i, M. daily while symptoms are present, followed by 50 mg. weekly through 1st trimes- ter, or until fetal vlability is evident.
Habitual abortion 1st trim.	10 mg. daily.	50 mg. I.M. weekly.
2nd trim.	20 mg. daily.	100 mg. 1.M. q. 2 wks.
3rd trim.	40 mg. daily, through 8th month.	100 mg. 1.M, q. 2 wks. through 8th month.
Supplied:	2.5 mg. scored, pink tab- lets, bottles of 25; 10 mg. scored, white tab- lets, bottles of 25 and 100.	Sterile aqueous sus- pension for intra- muscular use only. 50 mg. per cc., in 1 cc. and 5 cc. vials.†

Precautions: Clinically, Provera is well tolerated. No significant untoward effects have been reported. Animal studies show that Provera possesses adrenocorticoid-like activity. While such adrenocroticoid action has not been observed in human subjects, patients receiving large doses of Provera continuously for prolonged periods should be observed closely. Likewise, large doses of Provera have been found to produce some instances of female fetal masculinization in animals. Although this has not occurred in human beings, the possibility of such an effect, particularly with large doses over a long period of time, should be considered.

Provera, administered alone or in combination with estrogens, should not be employed in patients with abnormal uterine bleeding until a definite diagnosis has been established and the possibility of genital malignancy has been eliminated.

†Each cc. of Depo-Provera contains: Medroxyprogesterone acetate, 50 mg.; Polyethylene glycol 4000, 28.8 mg.; Polysorbate 80, 1.92 mg.; Sodium chloride, 8.65 mg.; Methylparaben, 1.73 mg.; Propylparaben, 0.19 mg.; Water for injection, q.s.

The Upjohn Company, Kalamazoo, Michigan

STRADEMARK, REG. U.S. PAT. OFF.

GUIDE to TOPICAL THERAPY of VA

INDICATIONS	SIGNS & SYMPTOMS	Rx
Senile Vaginitis (useful also in kraurosis vul- vae, urethral caruncles, labial adhesions in children)	Thin, excoriated mucosa; pro- fuse, irritating discharge, often serosanguineous (may be pu- rulent, blood-tinged); pain, itching, burning.	"Premarin" Vaginal Cream 0.625 mg. conjugated estro
		gens, equine/Gm., in a non- liquefying base.
Before and after vaginal surgery in postmenopausal patients		(Also contains spermaceti, cetyl al- cohol, white wax, glyceryl mono- stearate, propylene glycol mono- stearate, methyl stearate, phenyl mercuric acetate, sodium lauryl sul- fate, glycerin, liquid petrolatum, and FD&C yellow No. 5.)
Vulvovaginitis (as an adjunct to anti-infective or other supportive measures)	Pruritus, burning; inflammatory tissue reaction.	"Premaring H-C Vaginal Cream 0.625 mg. conjugated estrogens, equine and 1.0 mg, hydrocortisone (present as acetate)/Gm., in a nonliquefying base.
	*	(Also contains citric acid, sodium citrate, glycerin, spermaceti, cetyl alcohol, white wax, glyceryl monostearate, propylene glycol monostearate, methyl stearate, phenyl mercuric acetate, sodium lauryl sulfate, liquid petrolatum and D&C orange No. 3.)
Monilial Vaginitis (also as an adjunct in trichomoniasis, alone or accompanied by moniliasis)	Mild to severe pruritus is pre- dominant symptom; little or no leukorrhea. NOTE: Monilial vaginitis is frequently asso- ciated with diabetes mellitus.	"Vanay" Vaginal Cream 250 mg. Triacetin/Gm., in a nonliquefying base. (Also contains polyoxyethylene sor- bitan monostearate, glyceryl mono stearate, silicon dioxide and titan jum dioxide.

*Copies of this therapy guide - printed in a convenient reference form - are available on request to Ayerst Laboratories, 22 East 40th Street, New York 16, N. Y.

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**Note: within a tion, ma or a pro



VAGINAL DISORDERS*

THERAPEUTIC EFFECT

DOSAGE

AVAILABILITY

Provides tissue-building action of topical estrogen to help counteract senile tissue atrophy. Prompt healing and enhanced resistance to infection follow improvement in texture and vascularity of vaginal mucosa.

Average dosage: 2 to 4 Gm. daily depending on severity of infection, NOTE: Use in atrophic lesions of the vulva does not preclude necessity for careful diagnostic measures to eliminate possibility of neoplasia.

Combination package: No. 874 — Each contains $1\frac{1}{2}$ oz. tube with 15 disposable applicators. (Direction sheet for use also enclosed.)

Facilitates healing; helps restore atrophied, friable vaginal tissue to healthier, more normal state.

Average dosage: 2 to 4 Gm. daily approx, 10 days before and 10 days after surgery.



Anti-inflammatory and antipruritic effects of hydrocortisone provide prompt relief of initial distress; topical estrogen exerts specific action to elicit physiologic tissue response.

Average dosage: 2 to 4 Gm. daily. Continue for at least 7 to 10 days after symptoms subside.

Combination package: No. 216

-Each contains 1 oz. tube with
15 disposable applicators.

(Direction sheet for use also en-



Provides prolonged, continuous antifungal effect without local irritation—through unique enzyme-controlled action. Restores physiologic pH favorable to normal vaginal flora. Nonstaining, odorless.

Average dosage: 2 to 4 Gm. intravaginally at bedtime. During acute stage, apply twice daily (at bedtime and in the morning). Following response, continue bedtime application for a period of time to prevent recurrence. During pregnancy, recommended until 7th month.**

Combination package: No. 204 — Each contains $1\frac{1}{2}$ oz. tube with 15 disposable applicators. (Direction sheet for use also enclosed.)



^{**}Note: Occasionally a burning sensation follows the first few applications of "Vanay" Vaginal Cream, usually disappearing within a short period of time. This sensation, presumably emanating from the eroded surfaces as a result of fungus destruction, may be indicative of effective therapy. During "Vanay" therapy, it is suggested that patients wear cotton undergarments or a protective sanitary pad since "Vanay" is harmful or destructive to synthetic fibers such as Rayon, Nylon, or Dacron.

effective hormonanag

DELUTE

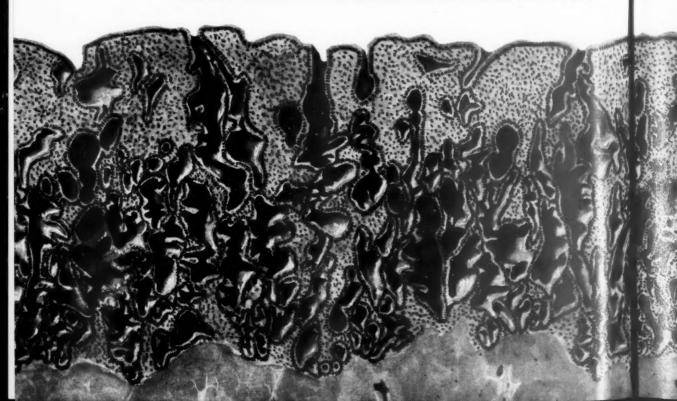
control of pain and bleeding by establishing pseudopregna, implifie

"The use of the mixture [Deluteval 2X] offers the definite advantage of a constancy of absorption as a result of parenteral administration. Injections may be spaced at intervals of 2 weeks and the dose held constant until 'breakthrough' bleeding occurs. The tendency toward nausea in the early part of the pseudopregnancy is diminished and the difficulties of oral administration are obviated. This progestin is a caproate ester of hydroxyprogesterone and is not a so-called '19-nor-compound'. Its androgenic potential is, therefore, less than that of some other available progestins. It is not contraindicated during early pregnancy."

"More recently, a still more convenient preparation has been used, Deluteval 2X... This conservative method of treating endometriosis with the prolonged administration of...Deluteval, in suitable...dosage, appears to afford fairly certain and rapid relief of the symptoms of the gynecologic disorder and to be free essentially from undesirable manifestations or complications." 2

1. Kistner, R. W.: The use of steroidal substances in endometriosis. Clin. Pharmacol. Therap. 1:525-537 (July-Aug.) 1960.

2. Thomas, H. H.: Conservative Treatment of Endometriosis. Obstet. and Gynecol. 15:498-503 (April) 1960.



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SQUIBB HYDROXYPROGESTERONE CAPROATE AND ESTRADIOL VALERATE

egna, implified injection treatment with long-acting ovarian hormones

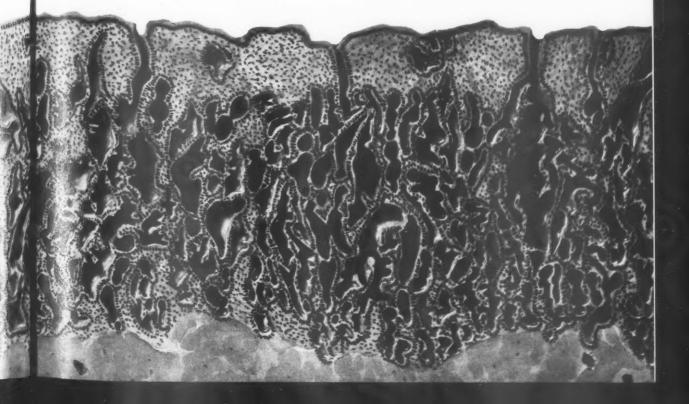
Dosage Schedule, Endometriosis — Deluteval 2X: 1 cc. or more, 2 days after ovulation; repeat once each week; raise by increments of 0.5 cc. every 6 weeks or whenever break-through bleeding occurs.

Precautions and Contraindications — Deluteval 2X should be administered with caution to patients in whom periodic attacks of asthma, migraine, or epilepsy are known to be exacerbated by progesterone. Estrogens are not recommended in premenopausal women with mammary carcinoma or genital malignancy.

Supply: Deluteval 2X: 5 cc. vials containing 250 mg. of hydroxyprogesterone caproate and 5 mg. of estradiol valerate per cc. May be stored at room temperature. Also available—Deluteval: 2 cc. ampuls containing 125 mg. hydroxyprogesterone caproate and 2.5 mg. estradiol valerate per cc.

For full information see your Squibb Product Reference or Product Brief.





Helps you take the misery out of menopause

as hormones alone often don't do



Fast-acting Milprem directly relieves both emotional dread and estrogen deficiency

Desage: One Milprem tablet t.i.d. in 21-day courses with one-week rest periods; during the rest periods, Miltown alone can sustain the patient.

Composition: Miltown (meprobamate) + conjugated estrogens (equine).

Supplied: Milprem-400, each coated pink tablet contains 400 mg. Miltown and 0.4 mg. conjugated estrogens (equine). Milprem-200, each coated old-rose tablet contains 200 mg. Miltown and 0.4 mg. conjugated estrogens (equine). Both potencies in bottles of 60.

Literature and samples on request.

Milprem

(Miltown® plus natural estrogens)

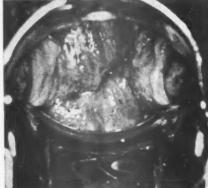
CHP-1806

Many physicians find that estrogen therapy is not enough for the woman who is also filled with anxiety by her menopause. Her emotional dread may make her so miserable that it becomes a real clinical problem.

This is where Milprem helps you so much. It calms the woman's anxiety and tension; prevents moody ups and downs; relieves her insomnia and headache. At the same time, it checks hot flushes by replacing lost estrogens. The patient feels better than she did on estrogen therapy alone. And your counsel and your assurances can now help her make her adjustment much faster.

WALLACE LABORATORIES / Cranbury, N. J.





monilial vaginitis

A COMMON PROBLEM
INCREASING
YEAR BY YEAR¹

Candidiasis is especially serious in diabetics...during pregnancy...in the debilitated... and when broad spectrum antibiotics have been administered in high dosage, with or without concurrent administration of cortisone or related steroids.

Clinical Results. In 26 patients (11 pregnant) with vaginal moniliasis, treatment with Mycostatin Vaginal Tablets was completely successful in 92% of cases. Marked to moderate improvement was shown in the remainder.²

In a series of 59 patients with candidiasis (31 pregnant), intravaginal therapy with Mycostatin proved 100% successful in the pregnant patients; similar response was shown in 96.3% of the nonpregnant cases.³

Supplied: Each Mycostatin Vaginal Tablet—individually foil wrapped, contains Mycostatin, 100,000 units, and lactose, 0.93 Gm. Packages of 15 with applicator. Also available: Mycostatin Oral Tablets... Ointment... Dusting Powder... Powder for Suspension... Cream.

References: 1. Lee, A. F., and Keifer, W. S.: Northwest Med. 53:1227 (Dec.) 1954. • 2. Caruso, L. J.: New York J. Med. 58:1688 (May 15) 1958. • 3. Pace, H. R., and Schantz, S. I.: J.A.M.A. 162:268 (Sept. 22) 1956.

For full information, see your Squibb Product Reference or Product Brief.

specific highly effective safe

Mycostatin VAGINAL TABLETS





Squibb Quality-the Priceless Ingredient

MYCOSTATIN'® IS A SQUIBB TRADEMARK.

IF YOUR OWN WIFE WERE A SPONTANEOUS ABORTER ... WHAT WOULD YOU DO, DOCTOR?

1,425 physicians answered this question by treating abortion-prone women in their own families with Hesper-C Prenatal. 1,248 successful pregnancies (87.6%) resulted.1

Fetal salvage rates as high as 95% have been achieved when hesperidin complex and ascorbic acid (as provided by Hesper-C Prenatal) were administered with the usual vitamin and mineral supplementation.2,3

Hesper-C Prenatal (hesperidin complex, ascorbic acid plus vitamin-mineral supplementation) provides an established therapy for the restoration and maintenance of capillary integrity. It thus helps protect the habitual aborter and every pregnant woman against the decidual bleeding and spontaneous abortion triggered by capillary fragility.

Reports on file at The National Drug Company; data available on request. 2. Javert, C.: Obst. & Gynec. 3:420, 1954.
 Greenblatt, R. B.: Obst. & Gynec. 2:530, 1953.

a precaution in every pregnancy a necessity in habitual abortion



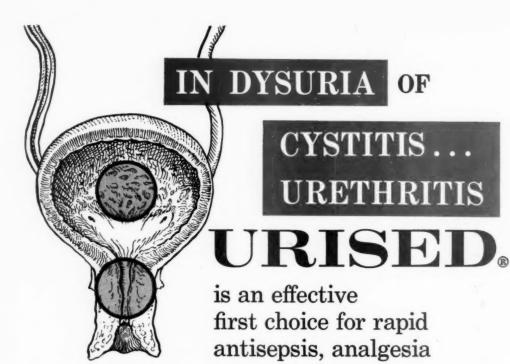
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THE NATIONAL DRUG COMPANY
Philadelphia 44, Pa.

HCP-1819/60 10/60

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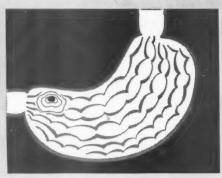
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